



King's Research Portal

DOI:

[10.1016/j.clnu.2017.06.025](https://doi.org/10.1016/j.clnu.2017.06.025)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Gomes, F., Schuetz, P., Bounoure, L., Austin, P., Ballesteros-Pomar, M., Cederholm, T., Fletcher, J., Laviano, A., Norman, K., Poulia, K-A., Ravasco, P., Schneider, S. M., Stanga, Z., Weekes, C. E., & Bischoff, S. C. (2017). ESPEN guidelines on nutritional support for polymorbid internal medicine patients. *CLINICAL NUTRITION*. <https://doi.org/10.1016/j.clnu.2017.06.025>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Accepted Manuscript

ESPEN guidelines on nutritional support for polymorbid internal medicine patients

Filomena Gomes, Philipp Schuetz, Lisa Bounoure, Peter Austin, María Ballesteros-Pomar, Tommy Cederholm, Jane Fletcher, Alessandro Laviano, Kristina Norman, Kalliopi-Anna Poulia, Paula Ravasco, Stephane M. Schneider, Zeno Stanga, C. Elizabeth Weekes, Stephan C. Bischoff



PII: S0261-5614(17)30236-4

DOI: [10.1016/j.clnu.2017.06.025](https://doi.org/10.1016/j.clnu.2017.06.025)

Reference: YCLNU 3182

To appear in: *Clinical Nutrition*

Received Date: 28 June 2017

Revised Date: 0261-5614 0261-5614

Accepted Date: 28 June 2017

Please cite this article as: Gomes F, Schuetz P, Bounoure L, Austin P, Ballesteros-Pomar M, Cederholm T, Fletcher J, Laviano A, Norman K, Poulia K-A, Ravasco P, Schneider SM, Stanga Z, Weekes CE, Bischoff SC, ESPEN guidelines on nutritional support for polymorbid internal medicine patients, *Clinical Nutrition* (2017), doi: 10.1016/j.clnu.2017.06.025.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ESPEN guidelines on nutritional support for polymorbid internal medicine patients

Filomena Gomes^{a1}, Philipp Schuetz^{a1*}, Lisa Bounoure^a, Peter Austin^b, María Ballesteros-Pomar^c, Tommy Cederholm^d, Jane Fletcher^e, Alessandro Laviano^f, Kristina Norman^g, Kalliopi-Anna Poulia^h, Paula Ravascoⁱ, Stephane M. Schneider^j, Zeno Stanga^l, C. Elizabeth Weekes^m, Stephan C. Bischoffⁿ

a - Cantonal Hospital Aarau and University of Basel, Switzerland

b - Oxford and Southampton University Hospitals, United Kingdom

c - Complejo Asistencial Universitario de León, Spain

d - Uppsala University, Sweden

e - Queen Elizabeth Hospital, Birmingham, United Kingdom

f - Sapienza University of Rome, Italy

g - Charité University Medicine Berlin, Germany

h - Laiko General Hospital of Athens, Greece

i - University of Lisbon, Portugal

j - University of Nice Sophia-Antipolis, France

l - University Hospital and University of Bern, Switzerland

m - Guy's & St. Thomas' NHS Foundation Trust and King's College London, United Kingdom

n - Institute of Nutritional Medicine, University of Hohenheim, Stuttgart, Germany

21 ¹ - F.G. and P.S. contributed equally to this study

22 * Corresponding author. Cantonal Hospital Aarau, Tellstrasse H7, 5001 Aarau and
23 Medical Faculty, University of Basel, Switzerland. Tel. +41628389524; Fax
24 +41628386945; e-mail address: philipp.schuetz@unibas.ch

Abstract

Background & Aims

Polymorbidity (also known as multimorbidity) - defined as the co-occurrence of at least two chronic health conditions - is highly prevalent, particularly in the hospitalized population. Nonetheless, clinical guidelines largely address individual diseases and rarely account for polymorbidity. The aim of this project was to develop guidelines on nutritional support for polymorbid patients hospitalized in medical wards.

Methods

The methodology used for the development of the current project follows the standard operating procedures for ESPEN guidelines. It started with an initial meeting of the Working Group in January 2015, where twelve key clinical questions were developed that encompassed different aspects of nutritional support: indication, route of feeding, energy and protein requirements, micronutrient requirements, disease-specific nutrients, timing, monitoring and procedure of intervention. Systematic literature searches were conducted in three different databases (Medline, Embase and the Cochrane Library), as well as in secondary sources (e.g. published guidelines), until April 2016. Retrieved abstracts were screened to identify relevant studies that were used to develop recommendations, which was followed by submission to Delphi voting rounds.

Results

From a total of 4532 retrieved abstracts, 38 relevant studies were analyzed and used to generate a guideline draft that proposed 22 recommendations and four statements. The results of the first online voting showed a strong consensus (agreement of >90%) in 68% of recommendations and 75% of statements, and consensus (agreement of >75-90%) in 32% of recommendations and 25% of statements. At the final consensus

conference, a consensus greater than 89% was reached for all of the recommendations.

Conclusions

Despite the methodological difficulties in creating non-disease specific guidelines, the evidence behind several important aspects of nutritional support for polymorbid medical inpatients was reviewed and summarized into practical clinical recommendations. Use of these guidelines offer an evidence-based nutritional approach to the polymorbid medical inpatients and may improve their outcomes.

Keywords

guidelines, polymorbidity, multimorbidity, nutritional support, hospitalized patients

Abbreviations

BI - Barthel Index

β HMB - β -hydroxy β -methylbutyrate

CG - Control Group

DRM - disease-related malnutrition

EN - enteral nutrition

GEB - Guidelines Editorial Board

IC - indirect calorimetry

IG - Intervention Group

LOS - length of hospital stay

MNA(-sf) - Mini Nutritional Assessment (short form)

- 71 NRS 2002 - Nutritional Risk Score 2002
- 72 ONS - oral nutritional supplement(s)
- 73 PICO - population of interest, interventions, comparisons, outcomes
- 74 PN - parenteral nutrition
- 75 QoL - quality of life
- 76 REE - resting energy expenditure
- 77 RCT - randomized controlled trial
- 78 SGA - Subjective Global Assessment
- 79 SIGN - Scottish Intercollegiate Guidelines Network
- 80 TEE - total energy expenditure
- 81 WG - Working Group

1. Introduction

1.1. What is the definition of polymorbidity?

Although there is no universally accepted definition of polymorbidity (also known as multimorbidity), some authors define it as being the co-occurrence of at least two chronic health conditions in the same person. That is also the definition used for the purposes of this guideline, based on literature recommendations [1-3] and discussions within the guideline Working Group (WG).

The health and nutrition implications of suffering from more than one disease at the same time differ from the corresponding interactions between disease and aging. Polymorbidity is often, but not necessarily, observed in older persons, in contrast to the geriatric context when multimorbidity is always combined with functional limitations and other age-related degenerative expressions. As life expectancy increases and individuals acquire a variety of chronic illnesses, polymorbidity becomes one of the main challenges that many healthcare and social services face worldwide.

1.2. Why do we need to develop nutritional support guidelines for polymorbid medical inpatients?

As stated by Lefevre et al., "we know, for example, how to educate a diabetic patient, a chronic bronchitis patient, and a hypertensive patient, but we do not know, in practical terms, how to educate a patient with all three diseases" [1]. In fact, we do not know if the screening, assessment and treatment of disease-related malnutrition (DRM) in polymorbid medical inpatients should differ from the approach used in patients with a single disease.

Polymorbidity is highly prevalent, affecting more than 70% of the hospitalized adult population, and is associated with higher mortality and healthcare burden [4]. Other consequences of polymorbidity include disability, functional decline, poor quality of life (QoL) and higher healthcare costs [3]. Whilst the prevalence increases with age, more than half of all people affected with this problem are younger than 65 years [5]. In this context, the current single-disease healthcare approach has been challenged, as clinical guidelines are largely created for individual diseases and rarely account for polymorbidity [5]. Fried et al. showed that clinicians struggle with the uncertainties of applying disease-specific guidelines to their patients with multiple conditions, and would therefore benefit from a number of tools to assist them in decision making for this population [6]. Limited, if any, accounting for polymorbidity applies to current nutritional guidelines that focus on single diseases (e.g. nutritional support in renal failure) or on patient groups (e.g. older adults). To date, it is unknown whether there is a synergistic negative effect of several diseases on nutritional status, or on clinical outcome. Therefore, there is a need for a consensus on how to provide nutritional support for the polymorbid medical inpatient population.

2. Materials and Methods

2.1. Pragmatic definition of polymorbidity for the current project

Guideline development is based on clinical trials that investigate the effects of screening and nutritional support on different outcomes. Because these population-based trials usually report an average number of comorbidities or number of drugs/medications, a pragmatic definition of the polymorbid inpatient population was established as:

- at least 2 co-occurring chronic diseases present in at least 50% of the study population (in a few of the studies it is stated that x% of the study population suffers from disease A, y% of the study population suffers from disease B, and so on)

or, alternatively,

- a Charlson comorbidity index in the study population as being more than 1.5
- a mean number of diseases or drugs (medications) over 1.5

In many studies, only this information is provided instead of the list of comorbidities and the proportion of the study population affected by each disease.

Polypharmacy is considered to be an important and acceptable marker of polymorbidity, with polypharmacy and polymorbidity having been described as being "two sides of the same coin" [7]. Additionally, it has been shown that the greater the number of medications, the higher the risk of weight loss [8], which suggests that polypharmacy has a potentially negative effect on nutritional status. The Charlson comorbidity index is the most extensively studied comorbidity index and is considered a valid and reliable method to measure comorbidity that can be used in clinical research [9].

In cases of uncertainty about the way that comorbidities were reported, the study authors were contacted in order to obtain additional information. In the event that they could not be reached a consensus decision within the guideline WG was taken about whether or not to include the study. Some of the included studies were conducted in older populations, since many polymorbid patients are also of an older age. For each included study, the criteria used to consider the study population as being polymorbid was recorded (and reported in the evidence table, in appendix 2).

2.2. Guideline development

The guideline WG was composed of a multidisciplinary team of 15 European specialists in nutritional support, who are the authors of the current paper. Following the standard operating procedures for the development of ESPEN guidelines [10], the guideline WG had an initial meeting in Zurich, in January 2015, to discuss the several stages of this project, and to define all of the clinical questions as well as the inclusion and exclusion criteria (table 1). Other relevant clinical questions which could not be developed in the "PICO" format (i.e. containing the 4 elements of population of interest, interventions, comparisons and outcomes (PICO)) have been included in the discussion.

Table 1 - Inclusion and exclusion criteria

Criteria	Inclusion	Exclusion
Patients characteristics	- Human adults aged ≥ 18 years	- Non human, ≤ 18 years, pregnant women
	- Patients hospitalized in acute care wards	- Patients admitted to critical/intensive care units - Surgical patients - Patients living on long-term care facilities - Outpatients - Patients receiving end of life care

	<p>- Polymorbid inpatients population as defined by</p> <p>a) at least 2 co-occurring chronic diseases are present in at least 50% of the study population</p> <p>or</p> <p>b) mean number of diseases or drugs/medication or the Charlson comorbidity index in the study population as being more than 1.5</p> <p>In case of uncertainties about the way comorbidities are reported, the trials' authors are contacted in order to get more information; if contact is not possible, the WG makes a consensus decision about the inclusion/exclusion of the studies.</p>	<p>- Healthy population</p> <p>- Less than 50% of the study population has 2 co-occurring diseases</p>
Outcomes	<p>Nutritional outcomes (e.g. weight, energy and protein intake)</p> <p>Clinical outcomes (e.g. mortality, infections)</p> <p>Patient-centred outcomes (e.g. quality of life)</p> <p>Healthcare resources</p>	
Language and year	English; no restriction on publication year	

Twelve questions in the PICO format covering nine topics of nutritional support (indication, route of feeding, energy and protein requirements, micronutrients requirements, disease-specific nutrients, timing, monitoring and procedure of intervention) were developed by the WG. These questions, the search key words proposed for each question, and the inclusion and exclusion criteria were discussed within the WG, and later approved by the ESPEN Guidelines Editorial Board (GEB).

A systematic literature search was conducted, first in secondary sources by searching published guidelines (e.g. from the National Institute for Health and Care Excellence, the Scottish Intercollegiate Guidelines Network (SIGN), the American Society for Parenteral and Enteral Nutrition) and systematic reviews potentially relevant for each question, followed by a search in primary sources. This primary sources search was

conducted by the same author in three databases (Medline, Embase and the Cochrane Library), until April 2016, using the GEB approved search terms proposed for each question. An example of a search strategy used can be found in Appendix 1 ("Search strategy used for question 2 in the Cochrane Library").

For each question, the results from each database were combined and exported to Endnote, followed by removal of duplicates and exportation to a Word document, allowing a single person (one of the WG coordinators) to undertake the screening of the final number of abstracts, in a standardized and systematic way.

Many studies required the assessment of the full paper to ascertain whether it met all of the inclusion criteria, and for a proportion of the papers (n=32), the authors were contacted and requested to provide more information, which was usually to clarify whether their study population suffered from multiple comorbidities. For those studies whose authors could not be reached (n=17), 11 were included and 6 excluded, as per the WG consensus decision.

Each WG member was allocated with one clinical question and was responsible for: validation of the literature, quality assessment and assignment of level of evidence for each paper relevant for the recommendations (e.g. using SIGN checklists), generation of first draft of recommendations, including the supporting text and grade of recommendation.

The classification of the literature into levels of evidence and grades of recommendation were performed according to the SIGN grading system [11], as exemplified in tables 2 and 3.

Table 2. Levels of evidence (SIGN grading system) [11]

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias.
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

201

202 **Table 3. Grades and forms of recommendations (SIGN grading system) [11]**

a. Grades of recommendation	
A	At least one meta-analysis, systematic review, or RCT rated as 1 ++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1 +, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2 ++, directly applicable to the target population; or A body of evidence including studies rated as 2 +, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1 ++ or 1 +
0	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2 ++ or 2 +
GPP	Good practice points / expert consensus: Recommended best practice based on the clinical experience of the guideline development group
b. Forms of recommendation	
Judgment	Recommendation
Undesirable consequences clearly outweigh desirable consequences	Strong recommendation against
Undesirable consequences probably outweigh desirable consequences	Conditional recommendation against
Balance between desirable and undesirable consequences is closely balanced or uncertain	Recommendation for research and possibly conditional recommendation for use restricted to trials
Desirable consequences probably outweigh undesirable consequences	Conditional recommendation for
Desirable consequences clearly outweigh undesirable consequences	Strong recommendation for

A total of 4532 abstracts were screened. The details of the primary searches can be found in table 4.

Table 4 - Number of abstracts retrieved for each question, in each database, and number of studies included for analysis

	Number of abstracts found in:				Included studies
	Medline	Embase	Cochrane Library	Total (without duplicates)	
Question 1	369	737	381	1401	2
Question 2	188	267	183	404	11
Question 3	318	532	327	859	1
Question 4	114	156	26	189	1
Question 5	162	220	82	395	2
Question 6	3	8	2	13	0
Question 7	116	174	102	223	2
Question 8	349	462	282	598	2
Question 9	6	4	10	19	10
Question 10	61	95	141	260	2
Question 11	18	23	7	25	2
Question 12	89	93	28	146	3

Thirty-eight studies were analyzed and included for the development of the recommendations. An evidence table with the number of studies allocated to each question, study details, evidence of polymorbidity for each study population, study type and level of evidence is presented in appendix 2 ("supplementary data: evidence table"). These studies can also be identified in the present document through the assignment of the respective evidence level in the text below each recommendation, in bold, e.g. "**Level of evidence 2+**".

The WG generated a guideline draft with a total of 22 recommendations and 4 statements (approved by the WG and the GEB office), which was followed by the start

of the consensus procedure, by sending that draft to the members of the ESPEN guideline project for online voting (Delphi method) in February 2017. The results of this online voting were a strong consensus (agreement of >90%) in 68% of recommendations and 75% of statements, and consensus (agreement of >75-90%) in 32% of recommendations and 25% of statements. None of the recommendations or statements reached an agreement of below 75%.

The feedback received during the online voting was used to modify and to improve the recommendations in order to reach a higher degree of acceptance at the final consensus meeting. The revised text was sent to the GEB office for approval.

The recommendations and statements with an agreement equal or lower than 90% were discussed in the final consensus meeting (organized by ESPEN), which took place in Frankfurt/Main, Germany, on the 24th April 2017. The consensus meeting was attended also by Cees Smith, who represented the patients interests and views. After the voting, all of the selected recommendations were discussed and amended as required, and consensus greater than 89% was reached for all of the recommendations.

3. Results

A summary of all of the clinical questions and the recommendations, including the grade of recommendation and level of consensus achieved at the final consensus conference, is presented in appendix 3 ("supplementary data: summary of clinical questions and recommendations").

Question 1. Does nutritional support based on screening and/or assessment versus no screening and/or assessment improve outcomes in polymorbid inpatients?

Recommendation 1.1.

In polymorbid medical inpatients, a quick and simple nutritional screening method using different validated tools should be applied to identify malnutrition risk. In patients at risk, a more detailed assessment should be performed and a treatment plan should be developed, to consent an early adequate nutritional therapy and to define quality outcome measures of success.

Grade of recommendation B - strong consensus (100% agreement)

Commentary:

Polymorbid medical inpatients are at high risk of malnutrition. Several prospective cohort studies showed a prevalence of approximately 40-50% in a hospitalized population of tertiary centers [12-14]. Observational studies have shown the frequency of complications in untreated at-risk patients to be three times higher than in patients not at-risk, and furthermore length of hospital stay (LOS) is 50% longer, which has a negative influence on clinical outcomes [15]. Scoring systems for determining nutritional risk, such as the Nutritional Risk Score 2002 (NRS 2002) and the Mini Nutritional Assessment (MNA-sf) link nutritional risk assessment to treatment by

predicting that nutritional interventions will have a positive influence on variable outcomes [16-19]. Both of these tools are rapid, easily undertaken and show a high degree of content validity and reliability, thereby making them suitable in polymorbid inpatients including those patients with cognitive dysfunction [20, 21]. If patients screen positive a more detailed assessment should be performed and a treatment plan should be developed. The effectiveness of the care plan should be measured by a subsequent monitoring including dietary intake, body weight, and measurements of mental and physical function and of clinical outcome.

In a controlled trial, Rypkema et al. demonstrated that a standardized, early nutritional intervention in older polymorbid inpatients at nutritional risk, determined by the MNA-sf, is effective and does not significantly increase hospital costs. The intervention resulted in both a more pronounced weight gain (0.92 ± 0.27 Kg in the intervention group (IG) vs. -0.76 ± 0.28 kg in the control group (CG), $p < 0.001$) and a significant lower rate of nosocomial infections (23.6% vs. 36.7%, $p = 0.01$) [22] **(Level of evidence 2+)**.

In a prospective, non-randomized cohort study, Jie et al. found nutritional support was beneficial for polymorbid inpatients at nutritional risk as defined by the NRS 2002 [13] **(Level of evidence 2+)**. The overall complication rate was significantly lower in the group with nutritional therapy than in the no-support group (20.3% versus 28.1%, $p = 0.009$), primarily because of the lower rate of infectious complications (10.5% versus 18.9%, $p < 0.001$). These effects were robust after multivariate adjustment. Also in the same study, the effects of each medical nutrition therapy were analyzed separately, and significantly lower complication rates were found only in patients who received enteral nutrition (EN) compared to the group without nutritional support (8.2% vs. 28.1%, $p < 0.001$).

Question 2. In polymorbid inpatients whose nutritional requirements can be met orally, does the use of oral nutritional supplements (ONS), with or without nutritional counseling, versus no ONS, improve outcomes?

Recommendation 2.1.

In malnourished polymorbid medical inpatients or those at high risk of malnutrition who can safely reach their nutritional requirements orally, ONS high in energy and protein shall be considered to improve their nutritional status and quality of life.

Grade of recommendation A - strong consensus (95% agreement)

Commentary:

Provision of ONS high in protein and energy in acutely ill hospitalized patients or inpatients at risk of developing malnutrition has been found to improve nutritional status. Hegerova et al. conducted a prospective randomized controlled trial (RCT) in 200 inpatients from an internal medicine department and found that the provision of ONS (combined with physiotherapy) increased the overall nutritional intake, mainly energy (1954 ± 429 Kcal in the IG vs. 1401 ± 364 Kcal, $p < 0.001$) and protein (76.3 in the IG ± 16.1 vs. 55.5 in the CG ± 13.7 , $p < 0.001$), without negatively affecting the hospital food consumption (72.8% in the IG vs. 71.3% in the CG, $p = 0.528$) [23] (**Level of evidence 1++**). This supplementation resulted in significant preservation of muscle mass (lean body mass difference between admission and 3 months after discharge was -3.5 Kg in CG patients, and $+1.3$ in the IG) and independence (the difference in the Barthel Index (BI) values between admission and 3 months showed a statistically significant decline in the CG ($p < 0.01$) vs. a non-significant decline in the IG).

Therefore, ONS have a supplemental role in the provision of nutrition during hospitalization.

Gariballa et al. found in a double blind RCT with 445 hospitalized patients that ONS provision significantly improved nutritional status (as indicated by the significant increase in serum albumin, red-cell folate and plasma vitamin B12 concentrations of the IG) and reduced the number of non-elective re-admissions in the 6-month follow-up period (adjusted HR 0.68, 95% CI 0.49-0.94) [24] **(Level of Evidence 1++)**. Similar results were also shown in other RCTs, where ONS provision (in addition to oxandrolone provided to both intervention and control groups) resulted in improvements of several parameters used to assess nutritional status, which were dependent on the level of DRM [25] **(Level of evidence 1-)**. Moreover, according to Starke et al., individualized nutritional support which included the provision of ONS in malnourished medical hospitalized patients resulted in improvement of their nutritional status (mean weight change from admission to discharge was 0.0 ± 2.9 kg in the IG vs. -1.4 ± 3.2 kg in the CG, $p=0.008$) and quality of life (Short Form-36 function summary scale was 37 ± 11 % in the IG vs. 32 ± 9 in the CG %, $p=0.030$), and reduction of complications during their hospital stay (4/66 in the IG vs. 13/66 in the CG, $p=0.035$) [19] **(Level of Evidence 1++)**. According to Volkert et al, provision of ONS to malnourished geriatric hospitalized patients resulted in improvements in nutritional status (e.g. in the IG with good acceptance, the mean weight gain was +0.4 kg, when compared with a loss of -1.6 kg in the IG with poor acceptance and -0.1 kg in CG) and recovery rate (e.g. in the IG with good acceptance, the proportion of independent patients (BI score >65 points) increased from 36% at admission to 63% at discharge and to 72% after 6 months, and was significantly higher compared to CG at discharge (19%, $p<0.05$) and after 6 months (39%, $p<0.05$)) [26] **(Level of Evidence**

2+). Lastly, according to Potter et al, in a RCT of 381 malnourished older hospitalized patients, the provision of ONS resulted in a reduction in unintentional weight loss ($p=0.003$), as well as in mortality (14.7% in the IG vs. 35% in the CG, $p<0.05$) when the analysis was confined to the severely undernourished group [27] **(Level of evidence 2++).**

Recommendation 2.2.

In malnourished polymorbid medical inpatients or those at high risk of malnutrition, nutrient-specific ONS should be administered, when they may maintain muscle mass, reduce mortality or improve quality of life.

Grade of recommendation B - consensus (89% agreement)

Commentary:

Several specialized nutrient specific ONS have been tested for their effectiveness on the improvement of outcomes in hospitalized patients. According to the NOURISH study, a multicenter RCT which included 652 malnourished inpatients, high protein – β -Hydroxy β -Methylbutyrate (β HMB) ONS may not yield a difference when compared with placebo on readmission rates, but may help with the maintenance of muscle mass during hospital stay and result in a significant decrease in post-discharge mortality (90-day mortality was 4.8% in the IG vs. 9.7% in the CG; RR 0.49 (95%CI 0.27 to 0.90), $p=0.018$) [28] **(Level of evidence 1++).** In addition, provision of ONS containing 995 Kcal from macronutrients and covering 100% of the RDA for healthy older adults in vitamins and minerals led to a lower incidence of depressive symptoms ($p=0.021$) in older medical inpatients, with no other effect on their cognitive performance but with a significant positive effect on their self-reported quality of life (i.e. the treatment effect in quality-of-life scores using the SF-36 form at 6 months was 7.0 (95%CI 0.5 to 13.6),

p=0.04 for physical function, 10.2 (95%CI 0.1–20.2), p=0.047 for role physical, and 7.8 (95%CI 0.0 to 15.5), p=0.05 for social function domains, compared to placebo).

[29, 30] **(Level of evidence 1++ for both)**. Although these results are interesting and promising, the available studies remain limited.

Recommendation 2.3.

In polymorbid medical inpatients who are malnourished or at high risk of malnutrition and can safely reach their nutritional requirements orally, ONS should be considered as a cost-effective way of intervention towards improved outcomes.

Grade of recommendation B - strong consensus (95% agreement)

Commentary:

Early detection and intervention against DRM has been shown to improve nutritional status and reduce complications during hospital stay [19] and non-elective re-admissions [24, 28] **(Level of Evidence 1++ for both)**. According to a cost-effectiveness analysis by Philipson et al., in a retrospective study from 2000 to 2010, the provision of ONS to malnourished medical inpatients resulted in a reduction in LOS of 2.3 days (95%CI –2.42 to –2.16) that subsequently decreased annual hospital costs by 4734\$ (95%CI –4754\$ to –4714\$), and reduced the readmission rate by 6.7%, from 34.3% to 32.0% [31] **(Level of evidence 2++)**. The greatest benefit was recorded in the most severely ill patients, which was a finding in general agreement with the "Feed Or Ordinary Diet" multi-center RCT, in which routine ONS (independent of baseline nutritional status) did not offer significant benefits to a mostly well-nourished stroke patient population (OR of death or poor outcome was 1.03 (95%CI 0.91 to 1.17) for the overall group and 0.78 (95% CI 0.46 to 1.35) in the small undernourished subgroup).

This stresses the importance of focusing nutritional support on those most in need [32]
(Level of Evidence 1++).

Question 3. In patients where nutritional requirements cannot be met orally, does the use of enteral nutrition (EN) compared to parenteral nutrition (PN) (total or supplemental) result in improved outcomes in polymorbid inpatients?

Recommendation 3.1.

In polymorbid medical inpatients whose nutritional requirements cannot be met orally, EN can be administered. In these cases, the use of EN may be superior to PN because of a lower risk of infectious and non-infectious complications.

Grade of recommendation 0 - strong consensus (100% agreement)

Commentary:

Reaching energy goals in medical inpatients is important to prevent weight loss and the loss of muscle mass that may lead to poorer functional outcomes. However, in the acute care setting many obstacles may prevent patients from meeting their nutritional requirements orally[33]. These obstacles include loss of appetite due to acute illness, delayed gastric emptying causing both nausea and early satiety, inability to swallow, and vomiting, among others. In these situations, use of EN or PN can help increase nutritional intake until oral intake is sufficient [34, 35]. Several randomized studies have compared the effect of nutritional support on outcomes of medical inpatients. A recent meta-analysis incorporating 22 RCTs conducted in medical inpatients found a significantly higher energy and protein intake, as well as beneficial effects on weight when comparing nutritional IG (including counseling and oral and enteral feeding) to CG [36]. When the analysis was restricted to the subgroup of malnourished patients, those receiving nutritional interventions had lower risk for readmission and shorter

hospital stays, but no significant effect on mortality, infections and functional outcomes was found. Other studies also used nutritional strategies with EN and/or PN compared to usual care or other feeding strategies in the medical inpatient setting [37-39]; these studies, however, did not directly compare the two feeding modalities. There are also several studies that investigated whether EN compared to PN resulted in better outcomes. While most studies examined the critical care setting [40] and patients with acute pancreatitis [41, 42], there is some observational evidence for the polymorbid medical inpatient population [13]. This observational evidence [13] consists of one large, prospective, non-randomized study (briefly described in the clinical question 1) from three Institutions in the US and China including patients at nutritional risk, as defined by the NRS 2002 score, that investigated the outcomes of patients receiving either EN or PN to patients without nutritional support [13] (**Level of evidence: 2+**). Approximately two thirds of the patients were medical patients from the department in respiratory and gastrointestinal diseases. Because the study was non-randomized, the authors used multiple logistic regression analysis to evaluate the influence of nutritional support on the risk of infectious and non-infectious complications. Overall, the study found a significantly lower risk of overall complications and infectious complications associated with nutritional support (adjusted OR 0.54 (95%CI 0.38 to 0.77), $p<0.001$ and adjusted OR 0.42 (95%CI 0.27 to 0.64), $p<0.001$, respectively). When the nutritional support group was further divided into those receiving PN and those receiving EN, the overall complication rate and the rates of infectious complications and non-infectious complications were significantly lower in those patients receiving EN than in those patients with no nutritional support ($p=0.001$). However, no difference in the complication rates were found between patients with PN and patients with no nutritional support ($p=0.29$). Because of differences in the patient

population, this analysis was also repeated in the patients undergoing major abdominal surgery who had PN or no nutritional support. Again, no significant difference in the complication rate was found between PN patients and control patients. This study has a number of important limitations regarding the observational, non-randomized design with important differences in study populations between PN and EN patients (as well as no-nutritional support patients), differences in hospital characteristics between the Chinese and the US hospitals and the lack of a standardized follow-up. Thus, causal inferences cannot be drawn. Still, the study suggests that EN may be more beneficial than PN, due to fewer infectious and non-infectious complications.

Although outside the scope of these guidelines, there is some evidence from critical care demonstrating that EN compared to PN results in lower complication risk; nonetheless, a recent meta-analysis including 30 RCTs did not find a mortality benefit [40]. In that meta-analysis, EN had a lower risk of both infectious complications (risk difference 8.8, 95%CI 0.0 to 17.5) and non-infectious complications (risk difference 12.2, 95%CI 4.6 to 19.9) in the sub-group of medical critical care patients. Similarly for pancreatitis, a meta-analysis including 6 trials found that compared with PN, EN was associated with a significantly lower incidence of pancreatic infection complications (RR = 0.556, 95%CI 0.436 to 0.709), multi-organ failure (RR = 0.395, 95% CI 0.272 to 0.573), surgical interventions (RR = 0.556, 95%CI 0.436 to 0.709), and mortality (RR = 0.426, 95%CI 0.238 to 0.764) [37].

In summary, high-quality randomized studies comparing EN and PN in the polymorbid medical inpatient setting are scarce. Still, when also considering high-quality evidence from critical care and in patients with pancreatitis as well as observational evidence from polymorbid medical patients, there are several arguments for the use of EN as a

first line therapy as compared to PN due to lower risks for infectious and non-infectious complications.

Question 4. Does the estimation of energy requirements with a prediction equation versus a weight-based formula improve outcomes of polymorbid inpatients requiring nutritional support?

Recommendation 4.1.

Energy requirements in polymorbid medical inpatients can be estimated using indirect calorimetry (IC), a published prediction equation or a weight-based formula.

Grade of recommendation 0 - strong consensus (96% agreement)

Recommendation 4.2.

In the absence of IC, total energy expenditure (TEE) for polymorbid older patients (aged > 65 years) can be estimated using the formula 27 kcal/kg actual body weight. Resting energy expenditure (REE) can be estimated using the formula 18 - 20 kcal/kg body weight with the addition of activity or stress factors to estimate TEE.

Grade of recommendation 0 - strong consensus (95% agreement)

Recommendation 4.3.a)

In the absence of IC, REE for severely underweight patients can be estimated using the formula 30 kcal/kg body weight.

Grade of recommendation 0 - consensus (agreement 89%)

Recommendation 4.3.b)

This target of 30 kcal/kg body weight in severely underweight patients should be cautiously and slowly achieved, as this is a population at high risk of refeeding syndrome.

Grade of recommendation GPP - strong consensus (agreement 100%)

Commentary:

The estimation of energy requirements is an important part of the patient assessment process and requires the determination of an individual's total energy expenditure (TEE) i.e. the sum of resting energy expenditure (REE), diet-induced thermogenesis and the energy expended during physical activity. The gold standard to measure REE is indirect calorimetry (IC) and for TEE the gold standard is doubly-labelled water. However, these methods are rarely available in the clinical setting and require considerable expertise [43]. Practitioners therefore tend to rely on either published prediction equations (e.g. Harris-Benedict [44] or Ireton-Jones [45]) or weight-based formulae (e.g. 25 – 30 kcal/kg body weight), to estimate energy requirements. In prediction equations, energy requirements are estimated from a number of different parameters e.g. weight, age, gender, ventilation status, heart rate etc.; in weight-based formulae the prediction is based solely on patient body weight. No single, validated method for estimating requirements exists, and the evidence-base for all prediction methods currently in use is poor [46]. In the absence of indirect calorimetry there is a debate about which of the two estimation methods is the most valid for use in the clinical setting. However, no studies were identified that answered this specific question.

While both published prediction equations and weight-based formulae provide valid estimates of energy requirements for groups of patients, both methods are subject to significant bias and imprecision when applied to individuals [47, 48]. More than 200 prediction equations have been published in the literature, with accuracy rates ranging from 36%–75% when compared with indirect calorimetry and no single equation emerges as being the most accurate in polymorbid medical inpatients [47].

Practitioners should therefore exercise a considerable degree of clinical judgment when determining the energy requirements of a polymorbid medical inpatient.

This also includes the choice of activity or stress factors, which relies on the clinical judgment, knowledge, and experience of the individual calculating the predicted requirements - it should be undertaken with caution since their misapplication can lead to clinically significant errors.

Individuals requiring nutritional support range from paralyzed and sedated, critically ill patients to fully mobile patients on the ward or in the community. To date, however, there is a relative lack of research on the effects of illness and injury on physical activity levels [49] although a recent consensus document concluded that since acute illness is usually accompanied by a decrease in physical activity that compensates for any increase in BMR, TEE is rarely above that of healthy, sedentary individuals of the same sex and age [50].

In a review designed to determine the energy requirements of frail older people [51], including polymorbid patients, 33 studies (2450 subjects) were identified where REE was measured by indirect calorimetry in subjects aged 65 years or more and the results were compared with healthy older individuals (**Level of evidence 2++**). Only studies that measured REE by IC after a fast and at rest were considered eligible for inclusion in the review. The mean age was 73.0 (± 6.6) years with no significant difference in BMI between the healthy and sick cohorts ($25.6 (\pm 1.5) \text{ kg/m}^2$ and $25.2 (\pm 2.5) \text{ kg/m}^2$ respectively) and no differences in fat mass or fat-free mass. The weighted mean for the whole group was 20.4 kcal/kg body weight whereas the weighted mean for the polymorbid hospitalized older group was lower at 18.5 kcal/kg body weight. The mean TEE in sick older individuals was 27 (± 1.8) kcal/kg body weight and the weighted physical activity level in these patients was 1.36 (± 0.03)

reflecting the relative physical inactivity of this population. The results of this review should be interpreted with caution since relatively few data were available in the sick older individuals (n=248) compared with the healthy older individuals (n=1970). Furthermore the methods described in the paper failed to comply fully with guidelines for the conduct of systematic reviews [52]. For example, only one database (MEDLINE) was searched when it is recommended that at least three should be searched, and only studies published in English were included.

In a study designed to evaluate the accuracy of prediction equations against IC in hospitalized patients [47], REE was measured by IC in 395 inpatients referred for nutritional support. REE measurements were compared with three prediction equations including one specifically for obese individuals [44, 45, 53] and one weight-based formula recommended by the American College of Chest Physicians (25 kcal/kg body weight). The mean age of the population was 56 (± 18) years and the mean BMI was 24 (± 5.6) kg/m². Measured REE was 1,617 (± 355) kcal/day for the entire group and 1,790 (± 397) kcal/day in the obese group (n=51). In this study the authors concluded that no single prediction equation was accurate (i.e. within 90-110% of measured REE) in the majority of the population.

In a study designed to determine the energy requirements of severely underweight hospitalized patients [54] energy expenditure was measured by IC in 14 patients. Mean BMI was 15.8 (± 1.8) kg/m² and mean age was 66.5 (± 13.9) years. In this study mean REE by IC was 1,300 (± 160) kcal/day equating to 31.4 kcal/kg body weight. These results should be interpreted with caution since the sample size was very small. Furthermore, patients received continuous EN or PN during IC and thus measured energy expenditure included not only REE but also diet-induced thermogenesis.

This target of approximately 30 kcal/kg body weight in severely underweight patients may need to be achieved with caution, as this is a population at high risk of refeeding syndrome. The diagnostic criteria and the factors proposed for screening of refeeding syndrome have been proposed elsewhere [55].

Clinicians should be aware of the limitations of using precise numbers on weight-based formulae (or prediction equations) since in all studies there is considerable variation around the effect estimate. They should recognize that all prediction methods are imprecise when applied to individuals and therefore should only be used as a starting point when estimating requirements. In fact, this highlights the need for input from a suitable and experienced healthcare professional to adequately assess the nutritional needs of the patient e.g. a dietitian.

From the review of the literature it is not possible to determine which method of estimating energy requirements (or which prediction equation) is the best in terms of promoting better outcomes in the polymorbid medical inpatient population.

Although the scope of this guideline is the general group of polymorbid patients, the available evidence for recommendation 4.2. is limited to the subgroup of polymorbid older patients. For further information regarding the nutritional care of older patients, please refer to the existing ESPEN guidelines on EN [56] and PN [57] for geriatric patients.

Question 5. Do protein targets higher than 1.0g/kg BW/day versus a lower target improve outcomes in polymorbid inpatients requiring nutritional support?

Recommendation 5.1.

Polymorbid medical inpatients requiring nutritional support shall receive a minimum of 1.0 g of protein/kg of body weight per day in order to prevent body

weight loss, reduce the risk of complications and hospital readmission and improve functional outcome.

Grade of recommendation A - strong consensus (95% agreement)

Commentary:

One high quality RCT [19] (**Level of evidence 1++**) and a subsequent secondary analysis of the same data [58] (**Level of evidence 1++**) compared the effect of protein intakes of 1g/Kg of patient's body weight per day versus lower intakes.

The trial by Starke et al. included adult patients hospitalized in a general medical ward, with a NRS score of 3 or more. The IG received 1 g of protein/kg of body weight per day in the form of individual food supply, fortified meals, in-between snacks and oral nutritional supplements for an average of 17.0 (± 10.4) days. The control group received standard nutritional care for an average of 18.6 (± 17.1) days, with a mean protein intake of 0.7g/kg of body weight per day.

At discharge, patients receiving 1 g of protein/kg of body weight per day (and significantly more energy) experienced less weight loss (0.0 (± 2.9) kg vs. -1.4 (± 3.2) kg, $p=0.008$), had an improved functional status (SF-36 function summary scale (37 (± 11) % vs. 32 (± 9) %, $p=0.030$), a lower risk for complications (4/66 vs. 13/66, $p=0.035$) and a reduced number of antibiotic therapies (1/66 vs. 8/66, $p=0.033$), compared to the CG patients receiving less protein [19]. Drommer and colleagues confirmed that the number of complications was inversely correlated with the mean daily protein intake ($p=0.017$). After 6 months, patients from the IG were less frequently readmitted to the hospital compared to the patients from the CG (17/64 vs. 28/61, $p=0.027$) [19].

Although these analyses were both undertaken using the same RCT patient data, the strong design and high methodological quality supports the recommendation to

provide at least 1 g of protein per kg of body weight in polymorbid inpatients. Recent guidelines from the American College of Gastroenterology about nutritional therapy in the adult hospitalized patients [41] suggest that protein targets as high as 1.5–2.0 g/kg body weight per day may even be needed to optimize nutritional support. In another recent publication evaluating practical procedures for nutritional support of medical inpatients, the authors investigated the question of protein intake targets needed to improve patients' outcomes. They used studies included in existing recommendations for particular diseases and medical specialties [34]. They also concluded that a minimum of 1.2 g of protein per kg of body weight per day is suitable for the vast majority of patients hospitalized in medical wards except for patients with renal impairment.

In the case of polymorbid medical inpatients with a renal condition, the amount of protein included in the daily nutritional plan may be different and should be cautiously assessed. Guidelines for renal patients recommend to lower the protein intake to 0.8-1 g/kg of body weight per day for at-risk or malnourished medical inpatients with acute and chronic renal failure and without renal replacement therapy [34, 59].

Our search did not yield any study assessing the effects of different protein intakes on outcomes of patients with clear evidence of kidney diseases in addition to one or several others. Therefore, it is not possible to know how the different diseases affecting polymorbid patients with a renal condition might interplay and to provide a recommendation in regard to protein intakes in polymorbid inpatients with a renal condition.

Question 6. In patients exclusively fed orally, does the supplementation of micronutrients (vitamins and trace elements)

compared to no supplements improve outcomes in polymorbid inpatients?

Recommendation 6.1.

In polymorbid medical inpatients exclusively fed orally adequate intake of micronutrients (vitamins and trace elements) to meet daily estimated requirements should be ensured.

Grade of recommendation GPP - strong consensus (100% agreement)

Recommendation 6.2.

Polymorbid medical inpatients exclusively fed orally with documented or suspected micronutrient deficiencies should be repleted.

Grade of recommendation GPP - strong consensus (93% agreement)

Commentary:

Polymorbid medical inpatients may be at risk of micronutrient deficiency as a result of decreased intake or greater micronutrient utilization, which can compromise health as well as recovery from illness or disease. The need for micronutrient supplementation is often based on clinical assessment of the subject and in some cases estimated daily micronutrient requirements may temporarily exceed recommended daily intakes in order to account for depleted stores and/or increased utilization (particularly in patients who are exclusively fed orally). For example, a study by Joosten et al. found hospital inpatients > 65 years of age likely to be deficient of vitamin B12, folate and/or vitamin B6, even though the same subjects had apparently normal reported levels of the same micronutrients [60]. A study by Kilonzo et al. [61] on self-reported morbidity from infections in free-living patients (rather than inpatients) aged > 65 years randomized to receive either a daily vitamin and mineral supplement or placebo found fewer QALYs per person in the supplemented group. This result is counter-intuitive, however

incomplete supplements not designed to replete micronutrient stores were used despite almost one third of the participants being judged at risk of micronutrient deficiency on recruitment. General micronutrient supplementation, with or without supplementation of specific micronutrients, based only on the provision of multivitamins rather than a combined multivitamin and multi-trace element appears to be common, and often based on financial cost of the supplement. However, if a subject may have general micronutrient depletion or generally increased micronutrient requirements then there is likely to be a need to provide trace elements as well as vitamins. Therefore, in the absence of specific toxicity risks or known micronutrient adequacy, supplementation should aim to deliver a complete range of both multivitamins and multi-trace elements rather than multivitamins alone. Complete micronutrient supplementation to meet reference nutrient intakes or otherwise estimated daily requirements could be particularly important in polymorbid inpatients due to the potential for any deficiencies to affect multiple and already compromised organ systems.

No studies were identified that reported the supplementation of multivitamins (with or without trace elements) compared to no supplements in polymorbid inpatients exclusively fed orally.

Question 7. Does disease-specific nutritional supplementation (e.g. fiber, omega 3 fatty acids, BCAA, glutamine, etc.) versus standard formulations improve outcomes in polymorbid inpatients?

Many specialized ONS/EN feeds have been developed for specific diseases that usually involve chronic/acute inflammation, specific micronutrient deficiency or specific metabolic disorders [62]. However, most studies were not conducted in identified

hospitalized polymorbid patients, even though some of these patients may well be polymorbid, and the number of usable studies identified was extremely low.

Recommendation 7.1.

In polymorbid medical inpatients with pressure ulcers, specific amino-acids (arginine and glutamine) and β -hydroxy β -methylbutyrate (β HMB) can be added to oral/enteral feeds to accelerate the healing of pressure ulcers.

Grade of recommendation 0 - consensus (90% agreement)

Commentary:

Pressure ulcers are responsible for protein loss, hypermetabolism and hypercatabolism, and are often associated with malnutrition, including nutrient deficiencies that are critical to the different phases of wound healing (conditionally essential amino acids and anti-oxidant micronutrients). A RCT from Singapore which included 26 polymorbid patients hospitalized for more than 2 weeks [63] showed a marginal albeit significant effect of an arginine/glutamine/ β HMB mixture on the healing of pressure ulcers (greatest improvement of viable tissues at two weeks in the IG, by 43% vs. 26%, $p=0.02$) (**level of evidence 1+**). The amino acid mixture (14 g arginine, 14 g glutamine and 2.4 g calcium β HMB per day) was not part of a nutritional formula, but all patients were fed per recommendations for hypermetabolic and hypercatabolic patients (30-35 kcal and 1.2-2.0 g protein/kg body weight/day according to the stage of the ulcer). As the basic nutritional needs were covered in both groups, the supplement (administered orally or enterally) was likely responsible for the beneficial effects observed.

Other positive studies have been published using an oral nutritional supplement enriched in arginine, zinc and anti-oxidants in patients outside the scope of these guidelines [64, 65].

Recommendation 7.2.

In polymorbid medical older inpatients requiring enteral nutrition, formulas enriched in a mixture of soluble and insoluble fibers can be used to improve bowel function.

Grade of recommendation 0 - strong consensus (95% agreement)

Commentary:

Diarrhea and constipation are the most frequent complications of EN in hospitalized patients. A Belgian study of 145 older patients receiving enteral feeding [66] found positive effects of a formula enriched with 30 g fiber including 33% insoluble (cellulose and hemicellulose A) and 67% soluble (pectin, hemicellulose B, inulin) fiber (IG) vs. the CG, which received the same EN with no fiber (**level of evidence 1++**). The frequency of stools was lower (4.1 ± 2.6 per week versus 6.3 ± 4.7 per week; $p < 0.001$) and the stool consistency higher in the IG (31% had solid form stools in the IG vs. 21% in the CG, and 2% had liquid-watery stool in the IG vs. 13% in the CG, $p < 0.001$); however, patients in the CG received more laxatives during the study period than patients in the fiber group. A global 4-week mortality of 24% underlines the severity of the patients' conditions.

The effects on bowel function associated with the absence of detrimental metabolic effect argue for a recommendation for a first intention use of EN formulae enriched with a mixture of soluble and insoluble fibers (supposed to match the multiple sources of fibers in normal food).

Recommendations 7.1 and 7.2 were downgraded from grade of recommendation B to 0, due to the limited amount of available studies.

Question 8. Does early nutritional support (i.e. provided less than 48 hours post hospital admission) compared to later nutritional support improve outcomes in polymorbid inpatients?

Recommendation 8.1.

Early nutritional support (i.e. provided in less than 48 hours post hospital admission) compared to later nutritional support should be performed in polymorbid medical inpatients, as sarcopenia could be decreased and self-sufficiency could be improved.

Grade of recommendation B - strong consensus (95% agreement)

Commentary:

Polymorbid medical inpatients are at high risk of developing DRM, so it is possible that this population could benefit from early nutritional support during hospital admission to avoid worsening of DRM with subsequent negative outcomes.

The use of early nutritional support is debated in different clinical scenarios and patient populations. Critically ill patients have been extensively studied, but still there is controversy. A recent meta-analysis conducted in populations with acute pancreatitis demonstrated that early EN was associated with significant reductions in infections, catheter-related septic complications, hyperglycemia, length of hospitalization and mortality, but the studies included did not show evidence of polymorbidity [67]. In one of the "Feed Or Ordinary Diet" trials [68], early tube feeding, defined as "as soon as possible", vs. avoiding any enteral tube feeding for at least seven days, was associated with an absolute reduction in risk of death but again, it is not known whether this population (where stroke was the primary insult) was polymorbid.

From the available literature addressing this question in medical inpatient populations with confirmed polymorbidity, two studies were identified.

First, a prospective RCT from Heregova et al. [23] aimed to determine whether early nutritional therapy and exercise would influence the development of sarcopenia and impaired self-sufficiency during acute illness. Two hundred inpatients >78 years old were randomized to a CG receiving standard treatment or to an IG, which consisted of ONS (600 kcal, 20 g/d protein) added to a standard diet and a simultaneous intensive rehabilitation program from day 1 of hospitalization. The amount of lean body mass in CG patients decreased during their hospital stay but did not change in the IG. Three months post-discharge, lean body mass was 3.5 kg lower in the control group but only 0.4 kg lower in the treated group. Lean body mass did not reach its original value even 12 months post-discharge in the CG, but it did in the IG. Regarding self-sufficiency (measured by independency in the activities of daily living through the Barthel index), it diminished during the course of annual monitoring in both groups of patients, but the decline was sharper in the CG (**Level of evidence 1+**).

Second, Zheng et al. [69] compared early EN (started on first day, n=75) with "family managed nutrition" (n=71) in a RCT of patients with acute stroke and dysphagia. The infection rate in the IG was significantly lower than that in the CG (33.3% vs. 52.1%, p=0.022). Also, the IG showed a better NIHSS score than that of the CG after 21 days (12.04 (± 2.55) vs. 10.78 (± 2.69); p=0.008). However, patients were admitted to the stroke unit in the IG and to the regular ward in the CG, which entails a high risk of bias (**Level of evidence 1-**).

Question 9. Does the continued use of nutritional support after discharge compared to nutritional support during inpatient stay alone affect the outcome of polymorbid patients?

For the present question, only interventions initiated in the hospital (and continued after discharge) were considered for inclusion. In case of doubt, authors were contacted to confirm this information.

Recommendation 9.1.

In malnourished polymorbid medical inpatients or those at risk of malnutrition nutritional support shall be continued after hospital discharge in order to maintain or improve body weight and nutritional status.

Grade of recommendation A - strong consensus (95% agreement)

Commentary:

Polymorbid medical inpatients are commonly malnourished and frequently nutritional status does not improve but instead deteriorates during their hospital stay. As a result, many patients leave the hospital malnourished, or more malnourished, which increases the risk for functional decline, loss of independence and greater morbidity. Poor nutritional status is acknowledged to contribute to the recently described post hospital syndrome that represents a 30-day “generalized transient vulnerability following hospital discharge” leading to higher morbidity and an increased rate of unplanned readmissions [70]. Therefore, ensuring adequate nutritional intake during the transition from hospital to home is an important goal in malnourished patients. Recent systematic reviews found evidence for improved body weight and nutritional status in older patients after discharge either with individualized nutritional support [71] or intervention with ONS [72]. Very few studies have, however, directly compared nutritional intervention in and after hospital discharge vs. nutritional support in hospital alone.

One study by Feldblum et al. which directly compared 6-month individualized nutritional support from a dietitian in hospital followed by three home visits after

discharge (group 1, n=66 (IG)) to either a single consultation with the dietitian in hospital or standard care (group 2 and 3, n=102 (CG)), showed that continued nutritional support in malnourished patients aged 65 or older resulted in a significantly higher change in mean MNA score, compared to the combined group 2 and 3 (3.01 (± 2.65) in the IG vs. 1.81 (± 2.97) in the CG, $p=0.004$) [73] **(Level of evidence 1-)**.

Similarly, in a prospective RCT of 80 patients aged 75 or more admitted for acute disease and at risk for malnutrition, a 60-day intervention with ONS which started in hospital and was continued at home or in the nursing home resulted in maintained body weight and improved MNA scores (3.01 (± 2.65) vs. 1.81 (± 2.97), $p=0.004$), whereas CG patients continued to lose weight [74] **(Level of Evidence 1++)**.

Similar results were obtained in other RCTs. In a RCT of malnourished hospital inpatients (47 in the IG and 46 in the CG) by Casals et al., the intervention resulted in increased body weight (4.750 (± 5.12) Kg in the IG vs. -0.903 (± 6.12) Kg in the CG, $p<0.001$) and improved the "Malnutrition Universal Screening Tool" score (-2.457 (± 1.39) in the IG vs. -1.170 (± 1.67) in the CG, $p<0.001$) after 6 months of continued nutritional counseling by case manager nurses (frequency of visits depending on severity of malnutrition, either every month or every second month) [75] **(Level of Evidence 1-)** and similarly, in a RCT of malnourished patients (according to the MNA-sf) aged 85 ± 6 years, individualized nutritional support for four months after discharge maintained body weight in the intention-to-treat analysis (difference in mean weight from baseline to 4-month follow-up was 0.6Kg in the IG vs. -1.5Kg in the CG, $p<0.001$), although a high dropout rate was reported [76] **(Level of Evidence 1+)**.

Recommendation 9.2.

In malnourished polymorbid medical inpatients or those at high risk of malnutrition, nutritional support should be continued post hospital discharge to maintain or improve functional status and quality of life.

Grade of recommendation B - strong consensus (95% agreement)

Commentary:

Improving functional status is one of the most important goals of nutritional therapy after discharge to prevent prolonged recovery, unplanned readmissions or loss of autonomy. Functional status can be assessed by objective measures such as hand grip strength or walking speed, or by subjective measures, for example through the use of questionnaires on mobility and physical ability. QoL is a multidimensional construct to evaluate the success of treatments which has been increasingly used in RCTs of nutritional interventions. Due to the many influencing factors on health-related QoL, sufficient sample sizes are needed and effects of nutritional therapy on QoL might depend on the subjects' age, the underlying disease or the duration of nutritional therapy.

In one RCT conducted in malnourished adults aged 60 or older admitted to an acute hospital for medical or surgical conditions, 3-month nutritional intervention (with energy and protein rich diets, ONS and calcium + Vit D supplements, providing 600 kcal/day and 24 g protein/day as well as 400 IE vitamin D3 and 500 mg calcium) resulted in a reduction in the number of falls (10% vs. 24%, $p=0.02$) [77] **(Level of Evidence 1++)**, significant improvement in self-reported functional limitations (mean difference -0.72, 95%CI -1.15 to -0.28) [78], and was neutral in financial cost [79] **(Level of Evidence 1++)**. On the other hand, increase in QoL did not differ between IG and CG receiving standard care [79] **(Level of Evidence 1++)**. In the study by Persson et al., which included old patients at risk of malnutrition (85 ± 6 years), treatment with complete or

incomplete liquid supplements (providing an average intake of 60 kcals and 11.25 g protein per day) and dietary advice for 4 months resulted in improvement of Katz activities of daily living index ($p<0.001$; $p=0.05$ between the groups), but not in QoL assessed by the 36-Item Short Form Health Survey [76] **(Level of Evidence 1+)**. On the other hand, Casals et al. reported significantly improved QoL scores (assessed by the Short Form 12 Health Survey, being the difference between IG and CG 13.72, $p<0.001$)) after 6 months of individualized nutritional support [75].

In younger malnourished patients (50.6 ± 16.1 years) with benign gastrointestinal or liver disease who received ONS during their hospital stay and for three months post discharge, QoL assessed by the 36-Item Short Form Health Survey questionnaire was significantly improved in the IG patients ($n=60$) compared to the CG patients ($n=54$) (mean improvement at 3 months was 0.128 (95%CI 0.095 to 0.161) in the IG vs. 0.067 (95%CI 0.031–0.103) in the CG) [80] **(Level of Evidence 1+)**. Grip strength and peak expiratory flow increased after three months only in the intervention patients (grip strength improved from 26.1 (± 11.3) to (31.5 ± 10.1) kg, $p<0.0001$; and peak flow from 329.2 (± 124.0) to 388.9 (± 108.4) l/min, $p=0.004$)) [81] **(Level of Evidence 1+)**.

Recommendation 9.3.

In polymorbid medical inpatients at high risk of malnutrition or with established malnutrition aged 65 and older, continued nutritional support post hospital discharge with either ONS or individualized nutritional intervention shall be considered to lower mortality.

Grade of recommendation A - strong consensus (95% agreement)

Commentary:

The effect of nutritional intervention with ONS on mortality has not been frequently studied in sufficiently sized patient cohorts. One of the largest RCTs to date ($n=652$

patients aged 65 years or more with medical conditions) on in- and post hospital (= continued) nutritional support reported lower 90-day mortality in the IG receiving ONS twice a day (one drink providing 350 kcal, 20 g protein, 1.5 g calcium- β HMB), 160 IU vitamin D and other essential micronutrients) for three months compared to the CG patients who received a placebo (4.8% in the IG vs. 9.7% in the CG, $p=0.018$) [28] **(Level of evidence 1++)**. In the study by Feldblum et al., the IG patients (>65 years) who received individualized nutritional support from a dietitian during hospitalization and for 6 month after discharge (three home visits after discharge) exhibited a significantly lower mortality rate (3.8%) than the CG (vs. 11.6%, $p=0.03$) at month 6 [73].

Although the scope of this guideline is the general group of polymorbid patients, the available evidence for recommendation 9.3. is limited to the subgroup of polymorbid older patients. For further information regarding the nutritional care of older patients, please refer to the existing ESPEN guidelines on EN [56] and PN [57] for geriatric patients.

The present recommendations highlight the need for ongoing review or monitoring nutritional support against patient specific goals post discharge (to establish whether continuation of medical nutrition therapy is needed) and the need for good quality communication of medical nutrition therapy regimens (whether oral, EN or PN) and goals of treatment in discharge documentation.

Question 10. Does the monitoring of physical functions, when it is possible, compared to monitoring of nutritional parameters (e.g. body weight, energy and protein intakes) improve other outcomes in polymorbid inpatients receiving nutritional support?

Recommendation 10.1.

Nutritional parameters should be monitored to assess responses to nutritional support, while functional indices should be used to assess other clinical outcomes (i.e., survival, quality of life) in polymorbid medical inpatients.

Grade of recommendation B - strong consensus (95% agreement)

Commentary:

Limited evidence exists to answer this clinical question precisely. Most trials assessing the impact of nutritional support in polymorbid inpatient used nutritional and functional status as outcome rather than as monitoring tools of the efficacy of nutrition intervention in improving other outcomes.

Mendehall et al. [25] studied 271 polymorbid inpatients with severe alcoholic hepatitis and randomly assigned to oxandrolone therapy plus a high-energy, high-protein supplement (active treatment) or placebo plus a low-energy, low protein supplement (standard treatment). Both groups initiated the nutritional support during hospitalization (30 days) and continued it at home when discharged (90 days). During hospitalization, patients in both groups were offered an identical hospital diet providing approximately 2500 kcal/d. Nutritional (i.e., body weight, triceps skinfold thickness), functional (i.e., handgrip strength) and clinical (i.e., laboratory tests) assessments were performed at baseline, after 1 month of hospitalization and after 2 months of outpatient therapy. Mendehall et al. also performed survival analysis at 6 months (i.e., 3 months after completion of nutrition therapy). All patients in both groups were malnourished. During treatment, energy and protein intake increased significantly in the active treatment group vs. standard treatment (2312Kcal vs. 1495Kcal ($p<0.001$) and 89g vs. 57g protein ($p<0.001$), respectively), leading to a significantly better mid-arm muscle area (change 4.5 vs. 0.3, $p=0.02$), creatinine-height index (change 18.4 vs. 2.6, $p=0.03$) and % ideal body weight (change 8.1 vs. 2.3, $p=0.04$). Interestingly, active treatment did

not improve handgrip strength better than standard treatment. However, when assessing the impact of nutrition intervention on 6-month mortality, Mendehall et al. reported that creatinine-height index, total lymphocyte count and handgrip strength are the stronger predictors. This suggests that although nutrition therapy improves nutritional status and outcome (i.e., they are tools to assess the response to therapy), functional parameters are more robust prognosticators of outcome. **(Level of evidence: 1-)**

Norman et al. [81] studied 80 malnourished polymorbid patients with gastrointestinal benign disease. After discharge from the hospital, patients were randomized into two groups: one group received for three months dietary counseling plus a standard oral nutritional supplement (IG) whereas the other group received only dietary counseling (CG group). At baseline, no difference was observed in nutritional (i.e., Subjective Global Assessment (SGA), body composition) and functional parameters (i.e., peak flow, handgrip strength) as well as in QoL (i.e., 36-item short form questionnaire) between the two groups. At the end of the study, both body weight and body cell mass improved significantly in both groups. However, handgrip strength (change from 26.1 to 31.5 kg, $p<0.0001$) and peak flow (change from 329.2 to 388.9 l/min, $p=0.004$) improved only in the IG. Also, all QoL subscales of 36-item short form questionnaire ($n=8$) significantly improved in IG patients, whereas only three (physical functioning, bodily pain and vitality) improved in CG patients. Of interest, the change in handgrip strength correlated with the change in two 36-item short form questionnaire physical scales (i.e., physical functioning and physical role). By applying the reasoning used for Mendehall et al.'s trial, it appears that Norman et al. confirm that functional parameters may be superior to nutritional parameters in assessing other clinical outcomes in polymorbid medical inpatients receiving nutritional support. **(Level of evidence: 1-)**

Supporting our interpretation of the available literature, Koretz et al. [82] analysed 99 RCTs of nutritional support vs. no nutritional support which reported at least one clinical outcome and at least one nutritional outcome. The authors' assumption was that if changes in nutritional markers predict clinical outcome, changes in both outcomes should go in the same direction. Therefore, the 99 clinical trials were assessed for concordance. The results showed that the rates of concordance were quite low and never >75%. The discordance was usually a result of the nutritional outcome being stronger than the clinical outcome. Koretz et al. then concluded that based on their analysis, changes in nutritional markers do not predict clinical outcomes. More recently, Jeejeebhoy et al. [83] prospectively studied 733 patients with complete nutritional intervention data to assess which nutrition indicator better predicts LOS and readmission within 30 days after discharge. After having controlled for age, sex, and diagnosis, only SGA C and reduced food intake during the first week of hospitalization resulted as independent predictors of length of stay. SGA C and hand grip strength but not food intake were independent predictors of 30-d readmission. This very recent study appears to suggest that nutritional parameters may serve well as monitoring tools to predict other clinical outcomes.

Question 11. Does meeting more than 75% of energy and/or protein requirements (as an indicator of compliance) versus a lower percentage improve outcomes in polymorbid inpatients receiving nutritional support?

Recommendation 11.1.

In polymorbid medical inpatients with reduced food intake and hampered nutritional status at least 75% of calculated energy and protein requirements should be achieved in order to reduce the risk of adverse outcomes.

Grade of recommendation B - strong consensus (100% agreement)

Recommendation 11.2.

Energy and protein fortified foods can be used in order to reach those relevant energy and protein targets in polymorbid medical inpatients.

Grade of recommendation 0 - strong consensus (100% agreement)

Commentary:

In polymorbid medical inpatients reduced food intake is more the rule than the exception [84] and is often an important part of the complex symptomatology that forces the patient to the hospital. Reduced food intake has several commonly occurring pathophysiologies including anorexia/reduced appetite, dysphagia or oral and dental problems. When reduced food intake is chronic or severe over longer and shorter periods of time, respectively, weight loss and malnutrition ensues. Since weight loss with malnutrition and reduced food intake are so closely linked it may be difficult to distinguish which of the syndromes are most detrimental for the patient. There are numerous studies indicating that reduced food intake is associated with increased mortality and with complications like infections in medical patients. For example, reports from the large database of the "NutritionDay" initiative demonstrate that reduced food intake during the day of food intake assessment is related to increased in-hospital mortality [85, 86]. Likewise, a study on approximately 1100 recently hospital-admitted patients with mixed diagnoses showed that 16% had a food intake below 70% of calculated energy requirement [87]. This energy intake was cross-sectionally associated with an increased risk of infections; adjusted odds ratio being 2.26 (95%CI 1.24 to 4.11).

In a good quality prospective observational study [88] (**Level of evidence 2++**), of close to 500 polymorbid patients admitted either to a medical service or to a surgical

service with mixed diagnoses, 21% had an average nutrient intake of less than 50% of calculated energy needs. Only patients with a hospital stay of more than four days were included in this study. Although baseline characteristics according to demography and diseases were quite similar, patients with reduced food intake had a higher in-hospital mortality as well as 90-day mortality with relative risks of 8.0 (95%CI 2.8 to 22.6) and 2.9 (95%CI 1.4 to 6.1), respectively.

Similar results were observed in a supportive study conducted in the critically ill population [89]. Twenty-eight day mortality was registered in a sequential series of 886 mechanically ventilated critically ill patients with both medical and surgical diagnoses where nutrition was provided either by the enteral (73%) or enteral combined with parenteral routes (26%). The energy target was guided by indirect calorimetry and protein target calculated as 1.2-1.5g/kg body weight/day. The group of the patients who received their target for both energy and protein needs had a 28-day mortality that was half that of those patients who did not achieve their target.

Thus, observational cohort studies clearly indicate that achieving goals for energy and protein intake during hospital stay is associated with better clinical outcomes. Such studies are unable to indicate whether or not the clinical outcome would be improved if sufficient nutrition could be provided. Such evidence can only be achieved by RCTs. A further question is what the optimal amount of nutrition is, or what is the least dose of nutrition needed to achieve potential beneficial effects. It has to be taken into account that an acute disease triggers inflammation and several catabolic processes in the body, which will hamper the body's capability to handle energy and protein for growth. Therefore, it is sometimes suggested (on expert opinion ground) that 75% of calculated needs could be a goal to achieve for energy and protein intake during the hospital stay and when the disease is still in an acute catabolic phase.

We aimed at finding studies that could answer the question: Does meeting more than 75% of energy and or protein requirements (as an indicator of compliance) versus a lower percentage improve outcomes in polymorbid inpatients receiving nutritional support? For this reason, we looked for RCTs in the literature. Unfortunately, no such studies were found. However, a Danish RCT [90] tested the hypothesis that protein fortification of a novel energy dense menu supplementary to the standard hospital food service could increase the food based nutrition intake of energy and protein beyond 75% of calculated requirements (**Level of evidence 1+**). The target population was newly-admitted polymorbid medical patients classified as at nutritional risk by NRS-2002. The RCT was well-conducted but too small for providing any evidence on clinical outcome measures. Altogether 81 patients fulfilled the study protocol. The novel menu consisted of protein fortified small energy dense dishes that could be ordered by telephone from the hospital kitchen by the patients from 7h to 22h. This intervention significantly improved the energy and protein intakes and also the number of patients that reached the protein target (calculated as 18% of energy intake), i.e. 66% reached the target compared to 30% in the control group. Handgrip strength and LOS were also reported but there were no differences to be observed, as expected when the study was not powered for such end-points.

Question 12. Do organizational changes in nutritional support (e.g. intervention of a steering committee, implementation of protected mealtimes, different budget allocation) versus no changes improve outcomes of polymorbid inpatients?

Recommendation 12.1.

Organizational changes in nutritional support provision should be implemented for polymorbid medical inpatients who are malnourished or at risk of

malnutrition. In particular, interventions that ensure the provision of fortified menus for at-risk patients, establishing a nutrition support team and the use of multi-disciplinary nutrition protocols should be implemented.

Grade of recommendation B - strong consensus (100% agreement)

Commentary:

The organization of nutritional support in hospitals requires a multi-disciplinary approach involving finance, catering, nursing and therapy services. Some studies have suggested that changes to the organization of nutritional support for in-patients may improve outcomes. One cohort study implemented the use of nutritional healthcare assistants. Medical patients who were deemed at high risk of malnutrition by the NRS 2002 were allocated a nutritional healthcare assistant, who was responsible for ensuring they received any necessary assistance to eat and drink and prepared individual meals for them. This study did not evaluate the impact on nutritional outcomes; however, the patient's perception of their nutritional care was improved and food wastage reduced [91]. Food fortification implemented in a non-randomized trial with medical, orthopedic and older inpatients, showed an increase in energy intake of 17.5% ($p=0.007$) over a 3-day recorded period [92]. Furthermore, collated results from three cross-sectional studies reported as one paper have suggested that introducing a nutrition screening tool and making changes to catering services may lead to a reduced prevalence of DRM across the general hospital population [93]. In this study, the investigators devised their own local nutrition screening tool as none was used at their organization prior to the intervention.

Despite these interesting studies in non-polymorbid patients, a systematic review of non-randomized studies showed that improvements are not consistently demonstrated. Forty-one studies were included in the review considering changes to

the organization of nutrition services, feeding environment and meal modification in hospital in-patients or those living in residential care. Due to the variability in reporting outcomes, it was not possible to assess the beneficial effects of specific interventions [94]. Therefore, it is important to consider the specific impact of organizational changes on polymorbid medical inpatients. From the identified literature, three studies were found. A single-blinded RCT [90] demonstrated how the use of a protein fortified menu was effective in increasing the protein intake of patients. Eighty-four patients were randomized to the study with a completion rate of 96%. The intervention group was able to choose from a protein enriched menu in addition to the standard hospital menu. The control group received the standard hospital menu. Patients were monitored for seven days. There was no significant difference in energy intake, length of stay or handgrip strength between the groups. However, mean protein intake was significantly increased in the IG; with 27/41 compared to 12/40 in the CG meeting $\geq 75\%$ protein requirements ($p=0.001$). Protein requirements were set at 18% of total energy requirements. Energy requirements were calculated by using the Harris-Benedict equation to estimate basal metabolic rate, which was then multiplied by a stress/activity factor according to Danish guidelines. **(Level of Evidence 1+)**

A further, prospective controlled trial [22] involving 298 polymorbid geriatric inpatients, demonstrated the use of an early multi-disciplinary intervention protocol. The protocol included activities such as nutrition and dysphagia screening, ensuring better patient positioning for mealtimes and individualizing time of meals. This was compared to standard care in the management of older patients at high risk of protein energy malnutrition across two sites. A significant weight gain (average 0.9 kg) was observed in the IG whereas a weight loss (average 0.8 kg) was observed in the CG, during admission. Mean LOS was approximately 32 days in both groups. In addition, the IG

developed fewer hospital acquired infections (33/140 compared to 58/158, $p=0.01$).

There was no statistically significant difference in the development of pressure ulcers or LOS. **(Level of Evidence 2+)**

Finally, a cohort study [95] demonstrated the impact of a nutrition support team on the management of patients requiring, or referred for, PN. Though the primary aim was to show cost- savings with nutrition support team management of PN, secondary clinical outcomes were also measured. Following a nutrition support team-lead, structured teaching program for nursing staff the catheter related sepsis rate in PN patients fell from 71% pre-NST to 29% in their first year ($p=0.05$). Additionally, 55 episodes of PN (41% of referrals) were avoided by appropriate nutrition support team assessment and rapid instigation of enteral feeding. **(Level of Evidence 2+)** Thus, the evidence shows that organizational changes in nutritional support provision can reduce the risk of adverse outcomes in polymorbid medical inpatients.

4. Discussion

Although the key areas of nutritional support in polymorbid medical inpatients were covered by the development of questions in the PICO format, there were a few clinical questions particularly relevant for the polymorbid inpatient population that were also developed by the WG but unable to be transformed into the required PICO format. These questions are presented below, with proposed statements (which were subjected to voting) and supportive text. These statements are informative points of the evidence rather than guides for action (i.e. they are not recommendations).

a) Does underlying disease have an impact on expected outcome from nutritional support?

Statement a.1.

The severity of acute-phase response may be used by clinicians as part of the criteria for selecting patients for nutritional screening, follow-up, and intervention.

Level of evidence 1+ - strong consensus (100% agreement)

Statement a.2.

Inadequate nutritional intake is common, and patient factors contributing to poor intake should be considered in designing nutritional interventions. Energy and protein intake are frequently inadequate to meet requirements in most older acute medical inpatients, worsening malnutrition during hospitalization and leading to poor outcomes. Poor intake is associated with several common patient/environmental characteristics, such as disease severity, symptoms compromising intake, anorexia, bedridden, hospital routines, dietary habits and possible therapeutic diets adopted at home.

Level of evidence 4 - strong consensus (100% agreement)

Commentary:

There are two main challenges in answering this question. One is the validity and reliability of nutritional assessment in acutely ill aging patients; the other is to understand if the relationship between poor nutritional status and acute-phase response is causal or an association.

Gariballa et al. [96] published a study in 2006 investigating the effects of the acute-phase response on nutritional status and clinical outcome of hospitalized medical polymorbid patients. The study was conducted in 445 patients in a double-blind RCT of nutritional supplementation and participants had their nutritional status assessed from anthropometric, hematologic, and biochemical data at baseline, 6 weeks, and 6 months. Outcome measures including disability, length of stay, and 1-year mortality were recorded. C-reactive protein concentration, a marker of acute-phase response, was also measured. Multivariate analysis was used to measure the association between acute-phase response and nutritional assessment variables after adjusting for age, disability, chronic illness, medications, and smoking. This study concluded that the acute-phase response is associated with poor nutritional status and poor clinical outcome in older patients. Yet, there was still an unanswered question which was whether nutritional support removes or mitigates the hazard of poor outcome associated with the acute-phase response. Confirmation of the relationship between underlying disease and expected outcome from nutritional support will need larger interventional studies to determine the optimal timing and composition of nutritional therapy relative to a patient's metabolic state.

In another paper, Mudge et al. [97] conducted a prospective study of patient factors associated with inadequate nutritional intake in older medical polymorbid inpatients, including 134 medical inpatients ≥ 65 years old. Primary outcome was energy intake

less than resting energy expenditure. Explanatory variables included age, gender, number of comorbidities, number of medications, diagnosis, usual residence, nutritional status, functional and cognitive impairment, depressive symptoms, poor appetite, poor dentition, and dysphagia.

b) How long should nutritional support be given in order to have an impact on the clinical course in a polymorbid inpatient?

Statement b.

Although there is evidence to recommend the continued nutritional support post-hospital discharge on polymorbid medical inpatients who are malnourished or at risk of malnutrition, the ideal duration of the intervention has not yet been determined.

Level of evidence 4 - strong consensus (95% agreement)

Commentary:

The ideal duration of post discharge nutritional intervention has not yet been determined but, in all likelihood, varies according to patients' age, underlying disease, initial nutritional status, type of nutritional support and endpoint of interest. In most RCTs on intervention with ONS, the sip feeds were given for three months [28, 77-81], whereas individualized nutritional support (which might include ONS where necessary) was usually carried out for longer periods (e.g. 4 months in the study by Persson et al. [76], or 6 months in the studies of Feldblum et al. [73] or Casals et al. [75]). Neelemaat et al. argue that while they were able to show an effect on functional limitations in their older intervention patients after three months, the length of nutritional support might not have been sufficient to show an effect on QoL [79]. Milne et al. also conclude in their systematic review on supplementation that the duration of treatment is frequently too short to expect any improvement in QoL or physical activities in older adults [98].

c) Are there risks of polypharmacy and drug-nutrient interaction in polymorbid inpatients?

Statement c.

In polymorbid medical inpatients there is an important possibility of drug-drug or drug-nutrient interactions that needs to be taken into account, by establishing a pharmacist-assisted management plan for any interactions.

Level of evidence 3 - consensus (90% agreement)

Commentary:

Polymorbid inpatients will often require the prescription of multiple medicines in order to manage their comorbidities. Whilst the use of multiple medicines is often essential, it can present a number of risks that include potential 'drug-drug' and/or 'drug-nutrient' interactions. Indeed, as the number of medicines required increases so does the risk of these interactions. Doses of medicines may need to be adjusted or other changes to the clinical management and monitoring of patients may be necessary, with examples including patients with co-morbidities in addition to human immunodeficiency virus infection [99, 100] or psoriasis [101]. It is, however, important that care is taken to not only consider interactions that may be more familiar. For example, many healthcare professionals are familiar with the physical binding of drugs such as tetracyclines to the divalent and trivalent cations found in milk or antacid preparations [102] or in many of the ONS and enteral formulas, which limits absorption from the gastrointestinal tract. Fewer are likely to be familiar with the potential for physical binding of ceftriaxone to calcium salts when each is given intravenously [103]. It is also important that care is taken to not only account for dietary intake but also oral fluid intake when considering potential drug-nutrient interactions. This is because whilst drugs such as simvastatin have no specific requirement to be taken with or without food it has the

potential to be toxic when taken concurrently with grapefruit juice [104]. Advice on the complexities of all of these potential interactions in polymorbid inpatients may be obtained from a pharmacist or a pharmacologist. We suggest that a review of medication is undertaken to identify unnecessary medications or medications that have side-effects which may compromise nutritional intake.

In summary, while some of the recommendations for screening, assessment and provision of nutritional support in polymorbid medical inpatients may not differ significantly from those recommendations applicable to single-disease patients, we have identified certain aspects of these patients' care that require particular attention, such as the identification of drug-drug or drug-nutrient interactions and the importance of continuing nutritional support after hospital discharge.

One of the strengths of this study was the conduct of the literature searches for all the clinical questions by a single author, which allowed the use of a systematic methodology to identify potentially relevant publications. This is particularly important for the present guidelines because, when compared to disease-specific guidelines, the methodology used for the identification of potentially relevant studies was more complex, as many of the published studies did not report data on the presence of multiple comorbidities or did not use typical key terms for this purpose. Additionally, there are no MeSH terms dedicated to multiple chronic conditions [1]. Consequently, we have not used search terms to define polymorbidity during the literature searches; instead we used different strategies to identify studies conducted in polymorbid populations, including the contact of authors to obtain further information on the presence of multiple comorbidities. In this context, we would encourage all authors of future trials to report data on polymorbidity.

1235 Furthermore, due to the complex nature of the needs of polymorbid medical inpatients,
1236 we would encourage access to dietetic expertise to assess, manage and monitor
1237 nutritional status and nutritional intervention, whenever possible. Community-based
1238 approaches are also encouraged for the non-hospitalized polymorbid patients at
1239 nutritional risk, allowing for prevention (of the deterioration of their nutritional status)
1240 and an early intervention.

5. Conclusions

Despite the methodological difficulties in creating non-disease specific guidelines, we managed to review the evidence behind several important aspects of nutritional support for polymorbid medical inpatients. This resulted in the development of 22 practical recommendations and four statements intended to guide clinicians working with this patient population. This work also allowed gaps in the literature (areas with little or no evidence) to be identified which require further research.

Acknowledgements

We thank the ESPEN committees (namely André Van Gossum, Pierre Singer, and Anna Schweinlin) for the continuous support during the development of the current guidelines. We also thank Cees Smith (patient representative) for his presence and helpful comments provided during the final consensus conference.

Funding:

This work was supported by the ESPEN society as well as by the SNF Swiss National Science Foundation (SNSF Professorship, PP00 P3_150531/1) and the Research Council of the Kantonsspital Aarau, Switzerland (1410.000.044).

Conflict of interest

FG - none

PS - received unrelated research support from Nestle and Abbott

1264 LB - none

1265 PA - none relevant to the present study.

1266 MBP - none

1267 TC - received unconditional grants from Nestlé, Nutricia.

1268 JF - none

1269 AL - honoraria for independent lectures at industry-sponsored educational and
1270 scientific events.

1271 KN - industry grants for clinical trials and received honoraria for independent talks.

1272 KAP - none

1273 PR - none

1274 SMS - consulting and/or lecturing and/or grants: B. Braun, Baxter, Fresenius-Kabi,
1275 Grand Fontaine, Nestlé, Nutricia

1276 ZS - did not receive any payment or support in kind for any aspect of the submitted
1277 work. Relevant financial relationships outside the submitted work: Research grants
1278 from Nestlé and Fresenius. Speaker honoraria from Nestlé, Fresenius and Abbott.
1279 Occasional adviser for Nestec and Abbott Switzerland.

1280 EW - none

1281 SB - none

References

- [1] Lefèvre T, d'Ivernois JF, De Andrade V, Crozet C, Lombrail P, Gagnayre R. What do we mean by multimorbidity? An analysis of the literature on multimorbidity measures, associated factors, and impact on health services organization. *Revue d'Épidémiologie et de Santé Publique*. 2014;62:305-14.
- [2] World Health Organization. The World Health Report 2008: primary health care (now more than ever). World Health Organization 2008.
- [3] Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A, et al. Aging with multimorbidity: A systematic review of the literature. *Ageing Research Reviews*. 2011;10:430-9.
- [4] Steiner CA, Friedman B. Hospital utilization, costs, and mortality for adults with multiple chronic conditions, Nationwide Inpatient Sample, 2009. *Preventing chronic disease*. 2013;10.
- [5] Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *The Lancet*. 2012;380:37-43.
- [6] Fried TR, Tinetti ME, Iannone L. Primary care clinicians' experiences with treatment decision making for older persons with multiple conditions. *Archives of Internal Medicine*. 2011;171:75-80.
- [7] Sinnott C, Bradley CP. Multimorbidity or polypharmacy: two sides of the same coin? 2015. 2015;5:3.
- [8] Agostini JV, Han L, Tinetti ME. The Relationship Between Number of Medications and Weight Loss or Impaired Balance in Older Adults. *Journal of the American Geriatrics Society*. 2004;52:1719-23.
- [9] de Groot V, Beckerman H, Lankhorst GJ, Bouter LM. How to measure comorbidity: a critical review of available methods. *Journal of Clinical Epidemiology*. 2003;56:221-9.
- [10] Bischoff SC, Singer P, Koller M, Barazzoni R, Cederholm T, van Gossum A. Standard operating procedures for ESPEN guidelines and consensus papers. *Clinical Nutrition*. 2015;34:1043-51.
- [11] Scottish Intercollegiate Guidelines Network (SIGN). SIGN 50: a guideline developer's handbook. Revised version. . Edinburgh 2014.
- [12] Gutzwiller J-P, Aschwanden J, Iff S, Leuenberger M, Perrig M, Stanga Z. Glucocorticoid treatment, immobility, and constipation are associated with nutritional risk. *European Journal of Nutrition*. 2011;50:665-71.
- [13] Jie B, Jiang Z-M, Nolan MT, Efron DT, Zhu S-N, Yu K, et al. Impact of nutritional support on clinical outcome in patients at nutritional risk: A multicenter, prospective cohort study in Baltimore and Beijing teaching hospitals. *Nutrition*. 2010;26:1088-93.
- [14] Felder S, Lechtenboehmer C, Bally M, Fehr R, Deiss M, Faessler L, et al. Association of nutritional risk and adverse medical outcomes across different medical inpatient populations. *Nutrition*. 2015;31:1385-93.
- [15] Sorensen J, Kondrup J, Prokopowicz J, Schiesser M, Krähenbühl L, Meier R, et al. EuroOOPS: An international, multicentre study to implement nutritional risk screening and evaluate clinical outcome. *Clinical Nutrition*. 2008;27:340-9.
- [16] Kondrup J, Rasmussen HH, Hamberg OLE, Stanga Z. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. *Clinical Nutrition*. 2002;22:321-36.
- [17] Patel C, Omer E, Diamond SJ, McClave SA. Can Nutritional Assessment Tools Predict Response to Nutritional Therapy? *Current Gastroenterology Reports*. 2016;18:15.
- [18] Rubenstein L, Harker J, Salvà A, Guigoz Y, Vellas B. Screening for undernutrition in geriatric practice: developing the short-form mini-nutritional assessment (MNA-SF). *J Gerontol A Biol Sci Med Sci*. 2001;56:M366-72.
- [19] Starke J, Schneider H, Alteheld B, Stehle P, Meier R. Short-term individual nutritional care as part of routine clinical setting improves outcome and quality of life in malnourished medical patients. *Clinical Nutrition*. 2011;30:194-201.

- [20] Hengstermann S, Nieczaj R, Steinhagen-Thiessen E, Schulz R. Which are the most efficient items of mini nutritional assessment in multimorbid patients? *J Nutr Health Aging*. 2008;12:117-22.
- [21] Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. ESPEN Guidelines for Nutrition Screening 2002. *Clinical Nutrition*. 2003;22:415-21.
- [22] Rypkema G, Adang E, Dicke H, Naber T, de Swart B, Disselhorst L, et al. Cost-effectiveness of an interdisciplinary intervention in geriatric inpatients to prevent malnutrition. *J Nutr Health Aging*. 2004;8:122-7.
- [23] Hegerová P, Dědková Z, Sobotka L. Early nutritional support and physiotherapy improved long-term self-sufficiency in acutely ill older patients. *Nutrition*. 2015;31:166-70.
- [24] Gariballa S, Forster S, Walters S, Powers H. A Randomized, Double-Blind, Placebo-Controlled Trial of Nutritional Supplementation During Acute Illness. *The American Journal of Medicine*. 2006;119:693-9.
- [25] Mendenhall CL, Moritz TE, Roselle GA, Morgan GA, Nemchausky BA, Tamburro CH, et al. Protein energy malnutrition in severe alcoholic hepatitis: diagnosis and response to treatment. *Journal of Parenteral and Enteral Nutrition*. 1995;19:258 - 65.
- [26] Volkert D, Hübsch S, Oster P, Schlierf G. Nutritional support and functional status in undernourished geriatric patients during hospitalization and 6-month follow-up. *Aging Clinical and Experimental Research*. 1996;8:386-95.
- [27] Potter JM, Roberts MA, McColl JH, Reilly JJ. Protein Energy Supplements in Unwell Elderly Patients—A Randomized Controlled Trial. *Journal of Parenteral and Enteral Nutrition*. 2001;25:323-9.
- [28] Deutz NE, Matheson EM, Matarese LE, Luo M, Baggs GE, Nelson JL, et al. Readmission and mortality in malnourished, older, hospitalized adults treated with a specialized oral nutritional supplement: A randomized clinical trial. *Clinical Nutrition*. 2016;35:18-26.
- [29] Gariballa S, Forster S. Dietary Supplementation and Quality of Life of Older Patients: A Randomized, Double-Blind, Placebo-Controlled Trial. *Journal of the American Geriatrics Society*. 2007;55:2030-4.
- [30] Gariballa S, Forster S. Effects of dietary supplements on depressive symptoms in older patients: A randomised double-blind placebo-controlled trial. *Clinical Nutrition*. 2007;26:545-51.
- [31] Philipson T, Snider J, Lakdawalla D, Stryckman B, Goldman D. Impact of oral nutritional supplementation on hospital outcomes. *American Journal of Managed Care*. 2003;19:121-8.
- [32] FOOD Trial Collaboration. Routine oral nutritional supplementation for stroke patients in hospital (FOOD): a multicentre randomised controlled trial. *The Lancet*. 2005;365:755-63.
- [33] Schuetz P. Food for thought: why does the medical community struggle with research about nutritional therapy in the acute care setting? *BMC medicine*. 2017;15:38.
- [34] Bounoure L, Gomes F, Stanga Z, Keller U, Meier R, Ballmer P, et al. Detection and treatment of medical inpatients with or at-risk of malnutrition: Suggested procedures based on validated guidelines. *Nutrition*. 2016;32:790-8.
- [35] Schuetz P. "Eat your lunch!" - controversies in the nutrition of the acutely, non-critically ill medical inpatient. *Swiss medical weekly*. 2015;145:w14132.
- [36] Bally MR, Blaser Yildirim PZ, Bounoure L, Gloy VL, Mueller B, Briel M, et al. Nutritional Support and Outcomes in Malnourished Medical Inpatients: A Systematic Review and Meta-analysis. *JAMA Intern Med*. 2016;176:43-53.
- [37] Johansen N, Kondrup J, Plum LM, Bak L, Norregaard P, Bunch E, et al. Effect of nutritional support on clinical outcome in patients at nutritional risk. *Clinical nutrition*. 2004;23:539-50.
- [38] Mulder POM BJ, Gietema JA, Van Rijsbergen H, Mulder NH, Van der Geest S, De Vries EGE. Hyperalimentation in autologous bone marrow transplantation for solid tumors *Cancer*. 1989;64:2045-52.
- [39] Somanchi M, Tao X, Mullin GE. The facilitated early enteral and dietary management effectiveness trial in hospitalized patients with malnutrition. *JPEN Journal of parenteral and enteral nutrition*. 2011;35:209-16.

- [40] Peter JV, Moran JL, Phillips-Hughes J. A metaanalysis of treatment outcomes of early enteral versus early parenteral nutrition in hospitalized patients. *Critical care medicine*. 2005;33:213-20; discussion 60-1.
- [41] McClave SA, DiBaise JK, Mullin GE, Martindale RG. ACG Clinical Guideline: Nutrition Therapy in the Adult Hospitalized Patient. *Am J Gastroenterol*. 2016;111:315-34.
- [42] Quan H, Wang X, Guo C. A Meta-Analysis of Enteral Nutrition and Total Parenteral Nutrition in Patients with Acute Pancreatitis. *Gastroenterology Research and Practice*. 2011;2011:9.
- [43] Branson RD, Johannigman JA. The measurement of energy expenditure. *Nutrition in clinical practice* : official publication of the American Society for Parenteral and Enteral Nutrition. 2004;19:622-36.
- [44] Harris JA, Benedict FG. A Biometric Study of Human Basal Metabolism. *Proceedings of the National Academy of Sciences of the United States of America*. 1918;4:370-3.
- [45] Ireton-Jones C. Comparison of the metabolic response to burn injury in obese and nonobese patients. *J Burn Care Rehabil*. 1997 18:82-5.
- [46] Reeves MM, Capra S. Predicting energy requirements in the clinical setting: are current methods evidence based? *Nutrition reviews*. 2003;61:143-51.
- [47] Boullata J, Williams J, Cottrell F, Hudson L, Compher C. Accurate Determination of Energy Needs in Hospitalized Patients. *Journal of the American Dietetic Association*. 2007;107:393-401.
- [48] Miles JM. Energy Expenditure in Hospitalized Patients: Implications for Nutritional Support. *Mayo Clinic Proceedings*. 2006;81:809-16.
- [49] Elia M. Insights into energy requirements in disease. *Public health nutrition*. 2005;8:1037-52.
- [50] Scientific Advisory Committee on Nutrition. Dietary reference values for energy. London: Public Health England; 2011.
- [51] Gaillard C, Alix E, Salle A, Berrut G, Ritz P. Energy requirements in frail elderly people: a review of the literature. *Clinical nutrition*. 2007;26:16-24.
- [52] Higgins J, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 [updated March 2011]: The Cochrane Collaboration; 2011.
- [53] Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. *The American Journal of Clinical Nutrition*. 1990;51:241-7.
- [54] Ahmad A, Duerksen DR, Munroe S, Bistrain BR. An evaluation of resting energy expenditure in hospitalized, severely underweight patients. *Nutrition (Burbank, Los Angeles County, Calif)*. 1999;15:384-8.
- [55] Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. *Clinical Nutrition*. 2017;36:49-64.
- [56] Volkert D, Berner YN, Berry E, Cederholm T, Coti Bertrand P, Milne A, et al. ESPEN Guidelines on Enteral Nutrition: Geriatrics. *Clinical Nutrition*. 2006;25:330-60.
- [57] Sobotka L, Schneider SM, Berner YN, Cederholm T, Krznaric Z, Shenkin A, et al. ESPEN Guidelines on Parenteral Nutrition: Geriatrics. *Clinical Nutrition*. 2009;28:461-6.
- [58] Drommer J, Schneider H, Alteheld B, Stehle P, Meier R. Protein is an important component of nutritional support predicting complications in malnourished hospitalised patients – Details of our previous randomised controlled trial (RCT). *Clinical Nutrition ESPEN*. 2015;10:e124-e8.
- [59] Cano N, Fiaccadori E, Tesinsky P, Toigo G, Druml W, Kuhlmann M, et al. ESPEN Guidelines on Enteral Nutrition: Adult Renal Failure. *Clinical Nutrition*. 2006;25:295-310.
- [60] Joosten E, van den Berg A, Riezler R, Naurath HJ, Lindenbaum J, Stabler SP, et al. Metabolic evidence that deficiencies of vitamin B-12 (cobalamin), folate, and vitamin B-6 occur commonly in elderly people. *The American Journal of Clinical Nutrition*. 1993;58:468-76.
- [61] Kilonzo MM, Vale LD, Cook JA, Milne AC, Stephen AI, Avenell A. A cost-utility analysis of multivitamin and multimineral supplements in men and women aged 65 years and over. *Clinical Nutrition*. 2007;26:364-70.

- [62] Zhu X-P, Zhu L-L, Zhou Q. Prescribing practice and evaluation of appropriateness of enteral nutrition in a university teaching hospital. *Therapeutics and Clinical Risk Management*. 2013;9:37-43.
- [63] Wong A, Chew A, Wang CM, Ong L, Zhang SH, Young S. The use of a specialised amino acid mixture for pressure ulcers: A placebo-controlled trial. *Journal of Wound Care*. 2014;23:259-69.
- [64] Cereda E, Klersy C, Seriola M, Crespi A, D'Andrea F, for the OligoElement Sore Trial Study G. A nutritional formula enriched with arginine, zinc, and antioxidants for the healing of pressure ulcers: A randomized trial. *Annals of Internal Medicine*. 2015;162:167-74.
- [65] Desneves KJ, Todorovic BE, Cassar A, Crowe TC. Treatment with supplementary arginine, vitamin C and zinc in patients with pressure ulcers: A randomised controlled trial. *Clinical Nutrition*. 2005;24:979-87.
- [66] Vandewoude MFJ, Paridaens KMJ, Suy RAL, Boone MAA, Strobbe H. Fibre-supplemented tube feeding in the hospitalised elderly. *Age and Ageing*. 2004;34:120-4.
- [67] Li J-Y, Yu T, Chen G-C, Yuan Y-H, Zhong W, Zhao L-N, et al. Enteral Nutrition within 48 Hours of Admission Improves Clinical Outcomes of Acute Pancreatitis by Reducing Complications: A Meta-Analysis. *PLoS ONE*. 2013;8:e64926.
- [68] Dennis M, Lewis S, Warlow C. Effect of timing and method of enteral tube feeding for dysphagic stroke patients (FOOD): a multicentre randomised controlled trial. *The Lancet*. 2005;365:764-72.
- [69] Zheng T, Zhu X, Liang H, Huang H, Yang J, Wang S. Impact of early enteral nutrition on short term prognosis after acute stroke. *Journal of Clinical Neuroscience*. 2015;22:1473-6.
- [70] Krumholz HM. Post-Hospital Syndrome — An Acquired, Transient Condition of Generalized Risk. *New England Journal of Medicine*. 2013;368:100-2.
- [71] Munk T, Tolstrup U, Beck AM, Holst M, Rasmussen HH, Hovhannisyan K, et al. Individualised dietary counselling for nutritionally at-risk older patients following discharge from acute hospital to home: a systematic review and meta-analysis. *Journal of Human Nutrition and Dietetics*. 2016;29:196-208.
- [72] Beck AM, Holst M, Rasmussen HH. Oral nutritional support of older (65 years+) medical and surgical patients after discharge from hospital: systematic review and meta-analysis of randomized controlled trials. *Clinical Rehabilitation*. 2013;27:19-27.
- [73] Feldblum I, German L, Castel H, Harman-Boehm I, Shahar DR. Individualized Nutritional Intervention During and After Hospitalization: The Nutrition Intervention Study Clinical Trial. *Journal of the American Geriatrics Society*. 2011;59:10-7.
- [74] Gazzotti C, Arnaud-Battandier F, Parello M, Farine S, Seidel L, Albert A, et al. Prevention of malnutrition in older people during and after hospitalisation: results from a randomised controlled clinical trial. *Age and Ageing*. 2003;32:321-5.
- [75] Casals C, García-Agua-Soler N, Vázquez-Sánchez MÁ, Requena-Toro MV, Padilla-Romero L, Casals-Sánchez JL. Randomized clinical trial of nutritional counseling for malnourished hospital patients. *Revista Clínica Española (English Edition)*. 2015;215:308-14.
- [76] Persson M, Hytter-Landahl Å, Brismar K, Cederholm T. Nutritional supplementation and dietary advice in geriatric patients at risk of malnutrition. *Clinical Nutrition*. 2007;26:216-24.
- [77] Neelemaat F, Lips P, Bosmans JE, Thijs A, Seidell JC, van Bokhorst-de van der Schueren MAE. Short-Term Oral Nutritional Intervention with Protein and Vitamin D Decreases Falls in Malnourished Older Adults. *Journal of the American Geriatrics Society*. 2012;60:691-9.
- [78] Neelemaat F, Bosmans JE, Thijs A, Seidell JC, van Bokhorst-de van der Schueren MAE. Post-Discharge Nutritional Support in Malnourished Elderly Individuals Improves Functional Limitations. *Journal of the American Medical Directors Association*. 2012;12:295-301.
- [79] Neelemaat F, Bosmans JE, Thijs A, Seidell JC, van Bokhorst-de van der Schueren MAE. Oral nutritional support in malnourished elderly decreases functional limitations with no extra costs. *Clinical Nutrition*. 2012;31:183-90.
- [80] Norman K, Pirlich M, Smoliner C, Kilbert A, Schulzke JD, Ockenga J, et al. Cost-effectiveness of a 3-month intervention with oral nutritional supplements in disease-related malnutrition: a randomised controlled pilot study. *European journal of clinical nutrition*. 2011;65:735-42.

- [81] Norman K, Kirchner H, Freudenreich M, Ockenga J, Lochs H, Pirlich M. Three month intervention with protein and energy rich supplements improve muscle function and quality of life in malnourished patients with non-neoplastic gastrointestinal disease—A randomized controlled trial. *Clinical Nutrition*. 2008;27:48-56.
- [82] Koretz RL. Nutrition Society Symposium on 'End points in clinical nutrition trials' Death, morbidity and economics are the only end points for trials. *Proceedings of the Nutrition Society*. 2005;64:277-84.
- [83] Jeejeebhoy KN, Keller H, Gramlich L, Allard JP, Laporte M, Duerksen DR, et al. Nutritional assessment: comparison of clinical assessment and objective variables for the prediction of length of hospital stay and readmission. *The American Journal of Clinical Nutrition*. 2015;101:956-65.
- [84] Schindler K, Themessl-Huber M, Hiesmayr M, Kosak S, Lainscak M, Laviano A, et al. To eat or not to eat? Indicators for reduced food intake in 91,245 patients hospitalized on nutritionDays 2006–2014 in 56 countries worldwide: a descriptive analysis. *The American Journal of Clinical Nutrition*. 2016;104:1393-402.
- [85] Hiesmayr M, Schindler K, Pernicka E, Schuh C, Schoeniger-Hekele A, Bauer P, et al. Decreased food intake is a risk factor for mortality in hospitalised patients: The NutritionDay survey 2006. *Clinical Nutrition*. 2006;28:484-91.
- [86] Lainscak M, Farkas J, Frantal S, Singer P, Bauer P, Hiesmayr M, et al. Self-rated health, nutritional intake and mortality in adult hospitalized patients. *European Journal of Clinical Investigation*. 2014;44:813-24.
- [87] Thibault R, Makhoulouf A-M, Kossovsky MP, Lavindrasana J, Chikhi M, Meyer R, et al. Healthcare-Associated Infections Are Associated with Insufficient Dietary Intake: An Observational Cross-Sectional Study. *PLoS ONE*. 2015;10:e0123695.
- [88] Sullivan DH, Sun S, Walls RC. Protein-energy undernutrition among elderly hospitalized patients: A prospective study. *JAMA*. 1999;281:2013-9.
- [89] Weijs PJM, Stapel SN, de Groot V, Driessen RH, de Jong E, Girbes ARJ, et al. Optimal Protein and Energy Nutrition Decreases Mortality in Mechanically Ventilated, Critically Ill Patients. *Journal of Parenteral and Enteral Nutrition*. 2012;36:60-8.
- [90] Munk T, Beck AM, Holst M, Rosenbom E, Rasmussen HH, Nielsen MA, et al. Positive effect of protein-supplemented hospital food on protein intake in patients at nutritional risk: a randomised controlled trial. *Journal of Human Nutrition and Dietetics*. 2014;27:122-32.
- [91] Lassen KO, Grinderslev E, Nyholm R. Effect of changed organisation of nutritional care of Danish medical inpatients. *BMC Health Services Research*. 2008;8:168.
- [92] Gall MJ, Grimble GK, Reeve NJ, Thomas SJ. Effect of providing fortified meals and between-meal snacks on energy and protein intake of hospital patients. *Clinical Nutrition*. 1996;17:259-64.
- [93] O'Flynn J, Peake H, Hickson M, Foster D, Frost G. The prevalence of malnutrition in hospitals can be reduced: Results from three consecutive cross-sectional studies. *Clinical Nutrition*. 2005;24:1078-88.
- [94] Kimber K, Gibbs M, Weekes CE, Baldwin C. Supportive interventions for enhancing dietary intake in malnourished or nutritionally at-risk adults: a systematic review of nonrandomised studies. *Journal of Human Nutrition and Dietetics*. 2015;28:517-45.
- [95] Kennedy JF, Nightingale JMD. Cost savings of an adult hospital nutrition support team. *Nutrition*. 2005;21:1127-33.
- [96] Gariballa S, Forster S. Effects of acute-phase response on nutritional status and clinical outcome of hospitalized patients. *Nutrition*. 2006;22:750-7.
- [97] Mudge AM, Ross LJ, Young AM, Isenring EA, Banks MD. Helping understand nutritional gaps in the elderly (HUNGER): A prospective study of patient factors associated with inadequate nutritional intake in older medical inpatients. *Clinical Nutrition*. 2011;30:320-5.
- [98] Milne AC, Potter J, Vivanti A, Avenell A. Protein and energy supplementation in elderly people at risk from malnutrition. *Cochrane Database of Systematic Reviews*. 2009.
- [99] Crespi-Lofton J. Managing clinically significant drug interactions in patients with HIV and comorbid conditions. *Pharmacy Today* 2016;64-76.

- 1552 [100] Tseng A, Foisy M, Hughes CA, Kelly D, Chan S, Dayneka N, et al. Role of the
1553 Pharmacist in Caring for Patients with HIV/AIDS: Clinical Practice Guidelines. 2012. 2012;65.
1554 [101] Sherin R, Udaykumar P. Assessment of Possible Drug Interactions in Patients with
1555 Psoriasis and Associated Comorbid Medical Conditions: An Observational Study. Reviews on
1556 Recent Clinical Trials 2016;11.
1557 [102] Neuvonen PJ. Interactions with the Absorption of Tetracyclines. Drugs. 1976;11:45-54.
1558 [103] Donnelly PC, Sutich RM, Easton R, Adejumo OA, Lee TA, Logan LK. Ceftriaxone-
1559 Associated Biliary and Cardiopulmonary Adverse Events in Neonates: A Systematic Review of
1560 the Literature. Pediatric Drugs. 2017;19:21-34.
1561 [104] Dreier JP, Endres M. Statin-associated rhabdomyolysis triggered by grapefruit
1562 consumption. Neurology. 2004;62:670.

Appendix 1 - Supplementary data: example of a search strategy

Search strategy used for question 2 in the Cochrane Library, on the 22nd April 2016

- #1 "oral nutrition* supplement*":ti,ab,kw (Word variations have been searched)
- #2 "oral nutrition* support"
- #3 energy near protein supplementation
- #4 "protein supplement*"
- #5 "energy supplement*"
- #6 "nutritional counseling"
- #7 "dietary advice"
- #8 "food fortification"
- #9 "food enrichment"
- #10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
- #11 MeSH descriptor: [Hospitals] 1 tree(s) exploded
- #12 hospital*:ti,ab,kw (Word variations have been searched)
- #13 "ward":ti,ab,kw (Word variations have been searched)
- #14 in?patient*:ti,ab,kw (Word variations have been searched)
- #15 #11 or #12 or #13 or #14
- #16 #10 and #15
- #17 MeSH descriptor: [Letter] explode all trees
- #18 MeSH descriptor: [Editorial] explode all trees
- #19 MeSH descriptor: [Case Reports] explode all trees
- #20 MeSH descriptor: [Animals] explode all trees
- #21 MeSH descriptor: [Child] explode all trees

1588 #22 MeSH descriptor: [Pediatrics] explode all trees
1589 #23 MeSH descriptor: [Pregnant Women] explode all trees
1590 #24 MeSH descriptor: [Outpatients] 1 tree(s) exploded
1591 #25 MeSH descriptor: [Ambulatory Care] explode all trees
1592 #26 MeSH descriptor: [Terminal Care] 2 tree(s) exploded
1593 #27 MeSH descriptor: [Palliative Care] 2 tree(s) exploded
1594 #28 letter or editorial or "case report" or "case study" or animal or rodent* or child* or
1595 infant or infancy or p?diatric* or pregnant or ambulatory or outpatient* or "nursing
1596 home*" or "long term care" or palliative or "end of life" or "terminal care" or animal* or
1597 rodent*
1598 #29 #17 or #18 or #19 #20 #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28
1599 #30 #16 not #29

Appendix 2 - Supplementary data: evidence table

Clinical question 1. Does nutritional support based on screening and/or assessment versus no screening and/or assessment improve outcomes in polymorbid inpatients?

Recommendation 1.1:

In polymorbid medical inpatients, a quick and simple nutritional screening method using a validated tool should be applied to identify malnutrition risk. In patients at risk, a more detailed assessment should be performed and a treatment plan should be developed to detect nutritional impairment, to consent an early adequate nutritional therapy and to define quality outcome measures of success.

Grade of recommendation B – strong consensus (100% agreement)

1. Rypkema G, Adang E, Dicke H, Naber T, De Swart B, Disselhorst L, Goluke-Willemsse G, Rikkert MO. Cost-effectiveness of an interdisciplinary intervention in geriatric inpatients to prevent malnutrition. Journal of Nutrition Health and Aging. 2004; 2: 122-127.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
prospective, controlled study 2+	<p>Countries: Netherlands</p> <p>Centers: The inpatient geriatric service of a university hospital (UMC Nijmegen) and a geriatric ward of a non-academic teaching hospital (Rijnstate Hospital, Arnhem)</p> <p>Setting:</p> <p>Funding Sources: research grant from the joint society of Dutch Universities (VAZ) and partly by Nutricia, Inc.</p> <p>Dropout rates:</p> <p>Study limitations: Missing data might have been caused by selection bias, intervention and control group were located in two separate geriatric units in two</p>	<p>Total no. patients: n = 298</p> <p>Inclusion criteria: All patients admitted to the geriatrics units (aged over 60 years) during a 10 month period in the year 2001 who were non-terminally ill and admitted for more than two days were eligible for inclusion</p> <p>Exclusion criteria: Patients admitted for over 150 days (and waiting for institutional care) were excluded from the study.</p>	<p>In order to reduce protein-energy malnutrition in older people during hospitalization, an early interdisciplinary intervention is needed. We developed a protocol which includes screening for malnutrition, dysphagia and dehydration on admission, followed by immediate interventions. One of the geriatric wards applied the protocol (N=140) while the other provided standard care (N=158).</p>

	different hospitals	
Notes	Author's Conclusion: An early interdisciplinary intervention approach can be effective in reducing protein-energy malnutrition and related hospital-acquired infections and appears to be economically feasible.	
Outcome measures/results	primary outcome measure: Weight, Body Mass Index (BMI), Barthel Index, MNA-sf, date of birth and sex, Nosocomial infections, pressure score, length of stay, edema, heart failure	There was a 0.8 kg loss (SEM 0.3 kg) in average weight in the standard care group and a 0.9 kg gain (SEM 0.2 kg) in the intervention group ($p < 0.001$). The number of hospital acquired infections was significantly lower in the intervention group (33/140 versus 58/158, $p = 0.01$) but no significant difference in number of patients with pressure sores (23/140 versus 33/158) was found. Costs were not significantly different: 7516 versus 7908 Euro/patient for intervention versus controls, respectively
Evidence of polymorbidity	Agreement within working group, following attempt to contact author	

1609

2. Jie B, Jiang Z, Nolan MT, Efron DT, Zhu S, Yu K, Kondrup J. Impact of nutritional support on clinical outcome in patients at nutritional risk: a multicenter, prospective cohort study in Baltimore and Beijing teaching hospitals. Nutrition. 2010; 11: 1088-1093.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
prospective cohort study 2+	Countries: China, United States Centers: three departments in Johns Hopkins Hospital in Baltimore, two teaching hospitals in Beijing Setting: Funding Sources: CSPEN, CMB and a grant from Wu JP Medical Research Foundation Dropout rates: appr. 5 % Study limitations:	Total no. patients: n = 1831 Inclusion criteria: medical patients with gastrointestinal disease or respiratory disease and surgical patients undergoing intra-abdominal surgery 1) age 18–80 y; 2) well oriented to time and place; 3) speaking/understanding English in the United States/Chinese in China 4) providing a written informed consent form; and 5) a hospital LOS of at least 4 d. Exclusion criteria: not specified	To evaluate the impact of nutritional support (PN and EN) on clinical outcomes in patients at nutritional risk defined by the Nutritional Risk Screening 2002.
Notes	Author's Conclusion: The preliminary results suggest that nutritional support (especially EN) is beneficial to patients nutritionally at risk as it is related to a lower complication rate, especially in those with obviously reduced oral intake. In contrast, nutritional support is not beneficial to the patients at no nutritional risk as defined by the NRS-2002.		
Outcome measures/results	primary outcome measure: nutritional status and disease severity, nutritional parameters, application of PN and EN, surgery, medication, complications and LOS	The overall complication rate was significantly lower in the nutritional-support group than in the no-support group, mainly because of the lower rate of infectious complications.	
Evidence of polymorbidity	Agreement within working group, following attempt to contact author		

1610

1611

1612

1613

1614

1615 **Clinical question 2. In polymorbid inpatients whose nutritional requirements can be met orally, does the use of oral nutritional supplements (ONS),**
1616 **with or without nutritional counseling, versus no ONS, improve outcomes?**

1617 **Recommendation 2.1:**

1618 **In malnourished polymorbid medical inpatients or those at high risk of malnutrition who can safely reach their nutritional requirements orally, ONS**
1619 **high in energy and protein shall be considered to improve their nutritional status and quality of life.**

1620 **Grade of recommendation A – strong consensus (95% agreement)**

1621 **Recommendation 2.2:**

1622 **In malnourished polymorbid medical inpatients or those at high risk of malnutrition, nutrient-specific ONS should be administered, when they may**
1623 **maintain muscle mass, reduce mortality or improve quality of life.**

1624 **Grade of recommendation B – consensus (89% agreement)**

1625 **Recommendation 2.3:**

1626 **In polymorbid medical inpatients who are malnourished or at high risk of malnutrition and can safely reach their nutritional requirements orally,**
1627 **ONS should be considered as a cost-effective way of intervention towards improved outcomes.**

1628 **Grade of recommendation B – strong consensus (95% agreement)**

3. Hegerová P, Dědková Z, Sobotka L. Early nutritional support and physiotherapy improved long-term self-sufficiency in acutely ill older patients. Nutrition. 2015; 1: 166-170.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
prospective, randomized controlled study 1++	Countries: Czech Republic Centers: Setting: Third Internal Department of Metabolic Care and Gerontology, Faculty Hospital in Hradec Králové Funding Sources: research grant PRVOUK P 37-12 Dropout rates: no dropout Study limitations:	Total no. patients: n = 200 Inclusion criteria: age >78 y, admission to the hospital as a result of acute illness, self-sufficiency of the patient before admission based on a Barthel Index (BI) score >60, and patient's consent to participate in the Study Exclusion criteria: terminal stage of disease, terminal organ failure, hospitalization in the previous 3 mo. or more than two hospitalizations in the previous 6 months, indication for immediate nutritional support (recent weight loss, reduced food intake of <50% of the normal amount for more than 2 d before admission, and body mass index [BMI] <18.5 kg/m2), low self-sufficiency before the acute disease (BI ≤ 60), advanced stage of dementia associated with loss of independence, and refusal to participate in the study	The aim of this study was to determine whether an active approach based on early nutritional therapy and exercise would influence the development of sarcopenia and impaired self-sufficiency during acute illness. The patients were randomized to a control group receiving standard treatment (n = 100) or to an intervention group (n = 100). The intervention consisted of nutritional supplements (600 kcal, 20 g/d protein) added to a standard diet and a simultaneous intensive rehabilitation program. The tolerance of supplements and their influence on spontaneous food intake, self-sufficiency, muscle strength, and body composition were evaluated during the study period. The patients were then regularly monitored for 1 y post discharge.
Notes	Author's Conclusion: The early nutritional intervention together with early rehabilitation preserves muscle mass and independence in ill older patients hospitalized because of acute disease.		
Outcome measures/results	primary outcome measure: Age, sex, diagnosis, number of hospitalization days, anthropometry, Body composition (lean tissue mass and adipose tissue), Self-sufficiency, Nutritional risk screening (NRS)	The provision of nutritional supplements together with early rehabilitation led to increased total energy and protein intake while the intake of standard hospital food was not reduced. The loss of lean body mass and a decrease in self-sufficiency were apparent at discharge from the hospital and 3 mo. thereafter in the control group. Nutritional supplementation and the rehabilitation program in the study group prevented these alterations. A positive effect of nutritional intervention and exercise during the hospital stay was apparent at 6 mo. post-discharge.	
Evidence of polymorbidity	Confirmed by author		

4. Gariballa S, Forster S. Dietary Supplementation and Quality of Life of Older Patients: A Randomized, Double-Blind, Placebo-Controlled Trial. J Am Geriatr Soc. 2007; 12:2030-2034.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
randomized controlled Trial 1++	Countries: United Kingdom Centers: Setting: Funding Sources: Health Foundation project grant Dropout rates: no dropouts Study limitations: improvement in quality-of-life scores as a result of nutritional support could be a chance finding; inclusion criteria and baseline characteristics suggest that the study population represented a better-nourished group of patients than those who were excluded because of severe illness or dementia	Total no. patients: n = 225 Inclusion criteria: aged 65 and older, in stable medical condition, and able to swallow and sign an informed written consent form Exclusion criteria: patients with severe medical or psychiatric illness, dementia, or malignancy and those living in an institution or already taking supplements	Normal hospital diet plus 400-mL oral nutritional supplements daily for 6 weeks. The composition of the supplement was such as to provide 995 kcal for energy and 100% of the Reference Nutrient Intakes for a healthy older person for vitamins and minerals.
Notes	Author's Conclusion: Oral nutritional supplementation of acutely ill hospitalized older patients led to a statistically significant benefit in quality of life.		
Outcome measures/results	outcome measure: Baseline, 6-week, and 6-month nutritional status and quality of life.	Randomization to the supplement group led to significantly better quality-of-life scores than in the placebo group at 6 months but not at 6 weeks, after adjustment for baseline quality of life, age, and sex. The effect of supplementation was seen in higher physical function, role physical, and social function scores. Corresponding treatment effects were 7.0 (95% confidence interval (CI) 50.5–13.6, P5.04), 10.2 (95% CI50.1–20.2, P5.047), and 7.8 (95% CI50.0 – 15.5, P5.05), respectively. There was no evidence of difference in Barthel scores at 6 months.	
Evidence of polymorbidity	Mean number of chronic diseases and drugs: 1.7 and 3.5 in the control group, respectively; 1.9 and 3.5 in the intervention group, respectively.		

5. Gariballa S, Forster S. Effects of dietary supplements on depressive symptoms in older patients: a randomised double-blind placebo-controlled trial. Clinical Nutrition. 2007; 5: 545-551.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
randomized controlled Trial 1++	Countries: United Arab Emirate, United Kingdom Centers: Setting: Funding Sources: The Health Foundation project grant Dropout rates: Study limitations: the decrease in depressive symptoms as a result of nutritional support could be a chance finding; follow-up assessments on depression, cognitive function and nutritional were only carried out on a sub-sample (51%) of study patients; inclusion criteria and baseline characteristics suggest that our study population represents a better-nourished group of patients	Total no. patients: n = 225 Inclusion criteria: age ≥ 65 years; stable medical condition; able to swallow and able to sign an informed written consent form Exclusion criteria: patients with severe medical or psychiatric illness, dementia (abbreviated mental test < 6), malignancy, living in institution and patients already on supplements	We randomly assigned 225 hospitalized acutely ill older patients to receive either normal hospital diet plus 400 mL oral nutritional supplements (106 subjects) or normal hospital diet plus a placebo (119 subjects) daily for 6 weeks. The composition of the supplement was such as to provide 995 kcal for energy and 100% of the Reference Nutrient Intakes for a healthy old person for vitamins and minerals.
Notes	Author's Conclusion: Oral nutritional supplementation of hospitalized acutely ill older patients led to a statistically significant benefit on depressive symptoms.		
Outcome measures/results	outcome measure: 6 weeks and 6 months changes in nutritional status, depressive symptoms and cognitive state.	Randomization to the supplement group led to a significant increase in red-cell folate and plasma vitamin B12 concentrations, in contrast to a decrease seen in the placebo group. There were significant differences in symptoms of depression scores in the supplement group compared with the placebo group at 6 months (p = 0.021 for between groups difference). The effect of supplement was seen in all patient groups including those with no symptoms of depression, mild depression and those with severe depression (p = 0.007). There was no evidence of a difference in cognitive function scores at 6 months.	
Evidence of polymorbidity	Mean number of chronic diseases and drugs: 1.7 and 3.5 in the control group, respectively; 1.9 and 3.5 in the intervention group, respectively		

6. Gariballa S, Forster S, Walters S, Powers H. A randomized, double-blind, placebo-controlled trial of nutritional supplementation during acute illness. Am J Med. 2006; 8: 693-699.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
randomized controlled trial 1++	Countries: United Arab Emirate Centers: Setting: Funding Sources: Dropout rates: no dropouts Study limitations: Our inclusion criteria and baseline characteristics suggest that our study population represent a better-nourished group of patients.	Total no. patients: n = 445 Inclusion criteria: age 65 years or more, able to swallow, and able to sign an informed written consent form Exclusion criteria: patients who had undergone gastric surgery, with diagnosed malabsorption or morbid obesity (BMI > 40), in a coma, with diagnosed severe dementia (abbreviated mental test < 6) and malignancy, living in an institution, and already taking supplements	We randomly assigned 445 hospitalized patients aged 65 to 92 years to receive either a normal hospital diet plus 400 mL oral nutritional supplements (223 subjects) or a normal hospital diet plus a placebo (222 subjects) daily for 6 weeks. The composition of the supplement was such as to provide 995 kcal of energy and 100% of the Reference Nutrient Intakes for vitamins and minerals for a healthy older person.
Notes	Author's Conclusion: Oral nutritional supplementation of acutely ill patients improved nutritional status and led to a statistically significant reduction in the number of non-elective readmissions.		
Outcome measures/results	outcome measure: 6 months of disability (Barthel score), non-elective readmission and length of stay in hospital, discharge destination (own home or institution), morbidity (infective complications), and mortality, nutritional status,	Randomization to the supplement group led to a significant improvement in nutritional status. Over 6 months, 65 patients (29%) in the supplements group were readmitted to the hospital compared with 89 patients (40%) in the placebo group (adjusted hazard ratio 0.68 [95% confidence interval 0.49-0.94]). The mean length of hospital stay was 9.4 days in the supplements group compared with 10.1 days in the placebo group. Thirty-two people (14%) died in the supplement group compared with 19 people (9%) in the placebo group at 6 months.	
Evidence of polymorbidity	Mean number of chronic diseases and drugs: 1.7 and 3.5 in the control group, respectively; 1.9 and 3.5 the intervention group, respectively		

7. Mendenhall CL, Moritz TE, Roselle GA, Morgan TR, Nemchausky BA, Tamburro CH, Schiff ER, McClain CJ, Marsano LS, Allen JI. Protein energy malnutrition in severe alcoholic hepatitis: diagnosis and response to treatment. J Parenter Enteral Nutr. 1995; 4: 258-265.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
intervention study 2+	Countries: Centers: eight Department of Veterans Affairs (DVA) Medical Centers. Setting: Funding Sources: Cooperative Studies Program of the Department of Veterans Affairs Medical Research Service. Dropout rates: no dropout Study limitations:	Total no. patients: n = 271 Inclusion criteria: Male patients with a clinical diagnosis of alcoholic hepatitis (AH), histologic confirmation of the etiology of the liver disease was not an absolute requirement so that severely ill patients with coagulopathy could be enrolled. Exclusion criteria: not mentioned	Protein energy malnutrition (PEM) was evaluated and expressed as percent of low normal in 271 patients initially, at 1 month and at 3 months. Active therapy consisted of anabolic steroid oxandrolone (OX) plus a high caloric food supplement vs a matching placebo and a low calorie supplement.
Notes	Author's Conclusion: Deterioration in nutritional parameters is a significant risk factor for survival in severe patients with alcoholic hepatitis. This deterioration is reversible with standard hospital care. Active therapy further improves creatinine height index, mid arm muscle area and total lymphocyte counts. Hence, these later parameters appear to be the best indicators for follow-up assessments.		
Outcome measures/results	outcome measure: Nutritional status, grip strength, immune status	Most of the parameters improved significantly from baseline on standard care; the largest improvement seen in visceral proteins, the smallest in fat stores (skinfold thickness). Total PEM score significantly correlated with 6 month mortality (p=0.0012). Using logistic regression analysis, creatinine height index, hand grip strength and total peripheral blood lymphocytes were the best risk factors for survival. When CD lymphocyte subsets replaced total lymphocyte counts in the equation, CD8 levels became a significant risk factor (p=.004). Active treatment produced significant improvements in those parameters related to total body and muscle mass (i.e., mid arm muscle area, p=0.02; creatinine height index, p=0.03; percent ideal body weight, p=0.04).	
Evidence of polymorbidity	> 2 co-occurring chronic diseases in > 50% of the study population		

8. Starke J, Schneider H, Alteheld B, Stehle P, Meier R. Short-term individual nutritional care as part of routine clinical setting improves outcome and quality of life in malnourished medical patients. Clinical nutrition. 2011; 2: 194-201.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
randomized controlled intervention study 1++	Countries: Germany and Switzerland Centers: Setting: Funding Sources: grants for clinical studies and education from Nestlé and from the Exchange Organisation StudEx/Switzerland and the German Academic Exchange Service (DAAD)/Germany Dropout rates: 50.5 % Study limitations: connected to study design: Preferred outcome parameters are often influenced by other factors than nutrition alone; our study was not powered to statistically confirm a causal relation to nutrition intervention	Total no. patients: n = 271 Inclusion criteria: Patients with a nutritional risk (NRS score ≥ 3) Exclusion criteria: no informed consent, terminal condition, expected stay <5 days (judged by physician), previous participation in this study, patient on starvation, on parenteral nutrition, and/or being on dialysis	132 risk patients defined by Nutritional Risk Screening 2002, were randomized to individualized nutrition support (intervention group [n = 66]) or standard hospital care (control group [n = 66]). The present study aimed at developing and evaluating a routinely manageable concept for an improved nutritional care of malnourished in-hospital patients.
Notes	Author's Conclusion: Malnourished patients profit from nutrition support regarding nutrition status and quality of life. They have fewer complications, need fewer antibiotics and are less often re-hospitalized.		
Outcome measures/results	primary outcome measure: average daily energy and protein intake secondary outcome measure: Body weight, plasma vitamin levels, quality of life, complications, antibiotic therapies, readmissions and mortality, number of complications, length of hospital stay, compliance with oral nutrition standard supplement consumption	Nutrition interventions led to higher intakes (mean [standard deviation]) in energy (1553 [341] kcal vs. 1115 [381] kcal, p < 0.001) and protein (65.4 [16.4] g vs. 43.9 [17.2] g, p < 0.001). Intervention patients (n = 66) kept their body weight in comparison to control patients (n = 66; 0.0 [2.9] kg vs. -1.4 [3.2] kg, p = 0.008). Positive effects on plasma ascorbic acid level (46.7 [26.7] mmol/l vs. 34.1 [24.2] mmol/l, p = 0.010), SF-36 function summary scale (37 [11] % vs. 32 [9] %, p = 0.030), number of complications (4/66 vs. 13/66, p = 0.035), antibiotic therapies (1/66 vs. 8/66, p ¼ 0.033) and readmissions (17/64 vs. 28/61, p = 0.027) were recorded.	
Evidence of polymorbidity	Mean number of drugs: 7 in the control group, 6 the intervention group		

9. Volkert D, Hübsch S, Oster P, Schlierf G. Nutritional support and functional status in undernourished geriatric patients during hospitalization and 6-month follow-up. <i>Aging Clinical and Experimental Research</i> . 1996; 6: 386-395.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
randomized controlled prospective intervention study 2+	<p>Countries: Germany</p> <p>Centers: Geriatisches Zentrum Bethanien am Klinikum der Universität Heidelberg</p> <p>Setting:</p> <p>Funding Sources: grants from the Bundesministerium für Gesundheit, Bonn and from Fa. B. Braun, Melsungen, Germany</p> <p>Dropout rates: 33.1 %</p> <p>Study limitations: The accepted amount of oral liquid supplements may be a limiting factor: Only one patient eventually accepted the total amount of 400 ml daily at hospital, and only half of the patients accepted supplements at home in the total amount.</p>	<p>Total no. patients: n = 72</p> <p>Inclusion criteria: female sex; age 75 years or older; undernourished by clinical judgment of the examining physician; no malignant disease; no need of tube-feeding or parenteral nutrition; expected hospital stay at least 3 weeks, and presumed actual life-expectancy of more than 6 months.</p> <p>Exclusion criteria: not mentioned</p>	<p>The objective was to evaluate the effect of nutritional supplementation on functional status and need of care in undernourished geriatric patients during hospitalization, and up to 6 months after discharge. Participants consisted of 46 undernourished geriatric patients from a geriatric acute care hospital aged 75 years or older without malignant disease, or need for tube feeding or parenteral nutrition. Patients in the supplement group (SG, N=20) were offered 400 mL (2100 kJ) daily of a liquid supplement during hospital stay and 200 mL (1050 kJ) per day for the following 6 months at home. Patients in the control group (CG, N=26) had usual care without supplements.</p>
Notes	<p>Author's Conclusion: A positive functional course was evident in supplemented patients with good acceptance during hospitalization, and further improvement was observed during the following 6 months at home. Nutritional support may contribute to reconvalescence and recovery of undernourished geriatric patients.</p>		
Outcome measures/results	<p>primary outcome measure: functional status based on the Barthel Activities of Daily Living score (ADL) at hospital admission, discharge and after 6 months</p> <p>secondary outcome measure: height, weight, BMI</p>	<p>In supplemented patients with good acceptance (SG+, N=11), a median improvement of 20 points was observed between admission and discharge, and a further improvement of 5 points at home. Median changes were 0 and -10 points in supplemented patients with poor acceptance (SG-, N=9) and 5 and 2.5 points in CG, respectively. In SG+, the proportion of independent patients (>65 points) increased continuously from 36% at admission to 63% at discharge, to 72% after 6 months, and was significantly higher compared to CG at discharge (63% vs 19%, $p<0.05$) and after 6 months (72% vs 39%, $p<0.05$). 64% of the patients in SG+ improved during hospitalization, compared to 23% in CG ($p<0.05$). In the six months at home, 18% of SG+ improved; none of SG+ deteriorated in hospital or at home. In contrast, deterioration of the ADL score occurred in considerable proportions of SG- (22% in hospital,</p>	

		22% at home) and CG (4% at hospital, 12% at home) patients. The proportion of patients who improved was smaller in SG- (44% at hospital, 22% at home) as well as in CG (23% at hospital, 35% at home), compared to SG+.
Evidence of polymorbidity	Reported in the paper: "All patients suffered from multiple diseases (...). The mean number of prescribed drugs was 2.4".	

10. Deutz NE, Matheson EM, Matarese LE, Luo M, Baggs GE, Nelson JL, Hegazi RA, Tappenden KA, Ziegler TR, NOURISH Study Group. Readmission and mortality in malnourished, older, hospitalized adults treated with a specialized oral nutritional supplement: a randomized clinical trial. Clinical Nutrition. 2016;1:18-26.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
Multicenter, randomized, placebo-controlled, double-blind trial 1++	Countries: USA Centers: Setting: Funding Sources: Abbott Nutrition Dropout rates: 4.9 % Study limitations: Limited generalizability; patients represent a selected hospitalized population.	Total no. patients: n = 652 Inclusion criteria: aged ≥ 65 years with a recent hospital admission (within 72 h) with a primary diagnosis of congestive heart failure, acute myocardial infarction, pneumonia, or chronic obstructive pulmonary disease. Patients were required to have a Subjective Global Assessment (SGA) class of B (moderate or suspected malnutrition) or C (severe malnutrition) Exclusion criteria: diabetes mellitus (type 1 or 2) due to product composition not intended for patients with diabetes mellitus; current active or treated cancer, and impaired renal or liver function	Evaluation of a high-protein oral nutritional supplement (HP-HMB) containing beta-hydroxybeta-methylbutyrate on post discharge outcomes of non-elective readmission and mortality in malnourished, hospitalized older adults. Standard-of-care plus HP-HMB (n = 328) or a placebo supplement (n = 324), 2 servings/day.
Notes	Author’s Conclusion: Although no effects were observed for the primary composite endpoint, compared with placebo HP-HMB decreased mortality and improved indices of nutritional status during the 90-day observation period.		
Outcome measures/results	primary outcome measure: 90-day post discharge incidence of death or non-elective readmission secondary outcome measure: 30- and 60-day post discharge incidence of death or readmission, length of stay (LOS), SGA class, body weight, and activities of daily living (ADL)	The primary composite endpoint was similar between HP-HMB (26.8%) and placebo (31.1%). No between-group differences were observed for 90-day readmission rate, but 90-day mortality was significantly lower with HP-HMB relative to placebo (4.8% vs. 9.7%; relative risk 0.49, 95% confidence interval [CI], 0.27 to 0.90; p = 0.018). The number-needed-to-treat to prevent 1 death was 20.3 (95% CI: 10.9, 121.4). Compared with placebo, HP-HMB resulted in improved odds of better nutritional status (SGA class, OR, 2.04, 95% CI: 1.28, 3.25, p = 0.009) at day 90, and an increase in body weight at day 30 (p = 0.035). LOS and ADL were similar between treatments.	
Evidence of polymorbidity	Mean Charlson comorbidity index: 2.05 in the control group, 2.12 in the intervention group.		

11. Philipson TJ, Snider JT, Lakdawalla DN, Stryckman B, Goldman DP. Impact of oral nutritional supplementation on hospital outcomes. Am J Manag Care. 2013; 2: 121-128.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
Eleven-year retrospective study 2++	Countries: USA Centers: Setting: Funding Sources: Abbott Nutrition Dropout rates: Study limitations: lack of detailed patient health information	Total no. patients: n = 44.0 million Inclusion criteria: adults 18 years or older Exclusion criteria: terminal episodes and all episodes involving tube feeding, leaving only oral feeding for examination	To assess the effect of inpatient oral nutritional supplement (ONS) use on length of stay, episode cost, and 30-day readmission probability. Analyses were conducted using the Premier Perspectives Database, which contained information on 44.0 million adult inpatient episodes.
Notes	Author's Conclusion: Use of ONS decreases length of stay, episode cost, and 30-day readmission risk in the inpatient population.		
Outcome measures/results	primary outcome measure: LOS, episode cost, and probability of 30-day readmission	Within the database, 1.6% of 44.0 million adult inpatient episodes involved ONS use. Based on a matched sample of 1.2 million episodes, ONS patients had a shorter length of stay by 2.3 days (95% confidence interval [CI] – 2.42 to –2.16), from 10.9 to 8.6 days (21.0% decline), and decreased episode cost of \$4734 (95% CI – \$4754 to – \$4714), from \$21,950 to \$17,216 (21.6% decline). Restricting the matched sample to the 862,960 episodes where patients were readmitted at some point, ONS patients had a reduced probability of early readmission (within 30 days) of 2.3 percentage points (95% CI – 0.027 to – 0.019), from 34.3% to 32.0% (6.7% decline).	
Evidence of polymorbidity	Mean Charlson comorbidity index: 3.5		

12. Potter JM, Roberts MA, McColl JH, Reilly JJ. Protein energy supplements in unwell elderly patients—a randomized controlled trial. J Parenter Enteral Nutr. 2001; 6: 323-329.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
randomized controlled trial 2++	Countries: Scotland Centers: Elderly Unit in a Scottish hospital Setting: Funding Sources: Chief Scientist's Office of Scottish Office; Fresenius UK Ltd provided the sip feed supplements free of charge. Dropout rates: no dropouts Study limitations:	Total no. patients: n = 381 Inclusion criteria: emergency admission from home; ability to gain consent from patient or relatives; no known malignancy, the ability to swallow, and non obesity (BMI < 75th percentile). Exclusion criteria: not mentioned	A prospective randomized controlled trial with no placebo. Consenting patients were stratified in 3 nutritional categories, and patients from each stratum were randomized into treatment or control. The intervention was a prescription of 120 mL sip feed, 3 times daily (540 kcal, 22.5 g protein per day) throughout hospitalization, using the medicine prescription chart
Notes	Author's Conclusion: Prescribing sip feed supplements in the medicine prescription chart during hospital stay reduces weight loss. Our data also support other evidence for a reduction in mortality noted in elderly patients on nutritional supplementation.		
Outcome measures/results	primary outcome measure: change in mean percentage weight secondary outcome measure: anthropometry; mortality, length of hospital stay, functional recovery, and rates of institutionalization.	Nutritional supplementation was associated with significantly better energy intake (p = .001) and weight gain (p = .003) pooled across all nutritional categories. In the most poorly nourished patients, the intervention was associated with reduced mortality (5/34 versus 14/40, p < .05) and more patients improved functionally (17/25 versus 11/28, p < .04). Overall mortality results were 21/186 versus 33/195, odds ratio (OR) 0.62, 95% confidence interval (CI) 0.35, 1.13.	
Evidence of polymorbidity	Agreement within working group, following attempt to contact author		

13. FOOD Trial Collaboration. Routine oral nutritional supplementation for stroke patients in hospital (FOOD): a multicentre randomised controlled trial. The Lancet. 2005; 9461: 755-763.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
randomized controlled trial 1+	<p>Countries:</p> <p>Centers:</p> <p>Setting:</p> <p>Funding Sources: Health Technology Assessment Board of NHS Research and Development in UK, the Stroke Association, the Chief Scientist Office of the Scottish Executive, and Chest, Heart and Stroke Scotland; The Royal Australasian College of Physicians</p> <p>Dropout rates: n = 11 (0, 3%)</p> <p>Study limitations:</p> <ul style="list-style-type: none"> -lack of masking treatment allocation to patients and hospital staff - very few patients in the normal-diet groups actually received supplements -missing record of the proportion of eligible patients enrolled in each centre -informal assessment of nutritional status -lack of verifying on-site source data -lack of report of total nutritional intake (e.g., composition of normal hospital diet) - normal hospital diets in the Centers may fully met the nutritional needs of the 	<p>Total no. patients: n = 4023</p> <ul style="list-style-type: none"> • Intervention n = 2016 • Control n = 2007 <p>Inclusion criteria: patients admitted with a recent stroke (first or recurrent stroke no more than 7 days before admission); passed swallow screen; enrolled within the first 30 days of admission, or within 30 days of a stroke occurring in hospital</p> <p>Exclusion criteria: Patients with subarachnoid hemorrhage</p>	<p>The aim of this study was to establish whether routine oral nutritional supplements improve outcome after stroke. The outcomes of stroke patients who could swallow and who were randomly allocated normal hospital diet or normal hospital diet plus oral nutritional supplements until hospital discharge.</p> <p>Intervention</p> <ul style="list-style-type: none"> - normal hospital diet plus oral protein energy supplements (equivalent to 360 mL at 6.27 kJ/mL and 62.5 g/L in protein every day) until discharge <p>Control</p> <ul style="list-style-type: none"> - normal hospital diet

	patients (and therefore inability to measure a large benefit occurred) - small proportion (8%) of undernourished patients at baseline might indicates that many such patients admitted to the hospitals were not enrolled but were given oral supplements outside the trial (because clinicians were not uncertain) -lack of report of information on nutritional outcomes (e.g., weight change during hospital stay)		
Notes	Author's Conclusion: We could not confirm the anticipated 4% absolute benefit for death or poor outcome from routine oral nutritional supplements for mainly well nourished stroke patients in hospital. Our results would be compatible with a 1% or 2% absolute benefit or harm from oral supplements. These results do not support a policy of routine oral supplementation after stroke.		
Outcome measures/results	Primary outcome measures: death or poor outcome (modified Rankin scale [MRS] grade 3–5), overall survival secondary outcome measures: place of residence, quality of life (EUROQoL score), compliance with treatment, length of hospital stay, discharge destination, in-hospital complications, causes of death	Between Nov 1, 1996, and July 31, 2003, 4023 patients were enrolled by 125 hospitals in 15 countries. Only 314 (8%) patients were judged to be undernourished at baseline. Vital status and MRS at the end of the trial were known for 4012 and 4004 patients, respectively. Supplemented diet was associated with an absolute reduction in risk of death of 0.7% (95% CI –1.4 to 2.7) and an increased risk of death or poor outcome of 0.7% (–2.3 to 3.8).	
Evidence of polymorbidity	Agreement within working group, following attempt to contact author		

1630

1631

1632

Clinical Question 3. In patients where nutritional requirements cannot be met orally, does the use of enteral nutrition (EN) compared to parenteral nutrition (PN) (total or supplemental) result in improved outcomes in polymorbid inpatients?

Recommendation 3.1:

In polymorbid medical inpatients whose nutritional requirements cannot be met orally, EN can be administered. In these cases, the use of EN may be superior to PN because of a lower risk of infectious and non-infectious complications

Grade of recommendation 0 – strong consensus (100% agreement)

14. Jie B, Jiang Z, Nolan MT, Efron DT, Zhu S, Yu K, Kondrup J. Impact of nutritional support on clinical outcome in patients at nutritional risk: a multicenter, prospective cohort study in Baltimore and Beijing teaching hospitals. Nutrition. 2010; 11: 1088-1093.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
prospective cohort study 2+	Countries: China, United States Centers: three departments in Johns Hopkins Hospital in Baltimore, two teaching hospitals in Beijing Setting: Funding Sources: CSPEN, CMB and a grant from Wu JP Medical Research Foundation Dropout rates: appr. 5 % Study limitations:	Total no. patients: n = 1831 Inclusion criteria: medical patients with gastrointestinal disease or respiratory disease and surgical patients undergoing intra-abdominal surgery 1) age 18–80 y; 2) well oriented to time and place; 3) speaking/understanding English in the United States/Chinese in China 4) providing a written informed consent form; and 5) a hospital LOS of at least 4 d. Exclusion criteria: not specified	To evaluate the impact of nutritional support (PN and EN) on clinical outcomes in patients at nutritional risk defined by the Nutritional Risk Screening 2002.
Notes	Author's Conclusion: The preliminary results suggest that nutritional support (especially EN) is beneficial to patients nutritionally at risk as it is related to a lower complication rate, especially in those with obviously reduced oral intake. In contrast, nutritional support is not beneficial to the patients at no nutritional risk as defined by the NRS-2002.		
Outcome measures/results	primary outcome measure: nutritional status and disease severity, nutritional parameters, application of PN and EN, surgery, medication, complications and LOS	The overall complication rate was significantly lower in the nutritional-support group than in the no-support group, mainly because of the lower rate of infectious complications.	
Evidence of polymorbidity	Agreement within working group, following attempt to contact author		

Clinical Question 4. Does the estimation of energy requirements with a prediction equation versus a weight-based formula improve outcomes of polymorbid inpatients requiring nutritional support?

Recommendation 4.1:

Energy requirements in polymorbid medical inpatients can be estimated using indirect calorimetry (IC), a published prediction equation or a weight-based formula.

Grade of recommendation 0 – strong consensus (96% agreement)

Recommendation 4.2:

In the absence of IC, total energy expenditure (TEE) for polymorbid older patients (aged > 65 years) can be estimated using the formula 27 kcal/kg actual body weight. Resting energy expenditure (REE) can be estimated using the formula 18 - 20 kcal/kg body weight with the addition of activity or stress factors to estimate TEE.

Grade of recommendation 0 – strong consensus (95% agreement)

Recommendation 4.3.a:

In the absence of IC, REE for severely underweight patients can be estimated using the formula 30 kcal/kg body weight.

Grade of recommendation 0 – consensus (89% agreement)

Recommendation 4.3.b:

This target of 30 kcal/kg body weight in severely under-weight patients should be cautiously and slowly achieved, as this is a population at high risk of refeeding syndrome.

Grade of recommendation GPP - strong consensus (100% agreement)

15. Gaillard C, Alix E, Salle A, Berrut G, Ritz P. Energy requirements in frail elderly people: a review of the literature. Clinical nutrition. 2007; 1: 16-24.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
Review 2++	Countries: France Centers: Setting: Funding Sources: Dropout rates: Study limitations: small number of subjects, limited number of data sets	Total no. patients: n = 248 from 11 studies Inclusion criteria: following studies were included: (1) those in which subjects had a minimal mean age of 60 yr or more with all being at least 55 yr of age, (2) those in which indirect calorimetry was performed while subjects were at rest and while fasting Exclusion criteria: Studies that included patients on specific diets, mechanically ventilated, cancer or burns patients or patients with thyroid problems and studies that did not mention the mean body weight of the studied group	This review collates studies of healthy, sick, underweight (BMI≤21 kg/m2) and very elderly people (≥90 yr), in whom resting energy expenditure (REE) was measured using indirect calorimetry.
Notes	Author's Conclusion: To conclude, REE, which can be used in conjunction with PAL to calculate energy requirements, is approximately 20 kcal/kg/d in sick elderly people. Further studies are needed in very elderly and sick people, taking their specific pathology into consideration.		
Outcome measures/results	outcome measure: different study outcomes; REE was measured in all studies	(1) REE, when adjusted for differences in both body weight and fat-free mass (FFM), is similar in healthy and in sick elderly people being 20 and 28 kcal/kg of FFM per day, respectively, (2) their nutritional status influences their energy requirements given that weight-adjusted REE increases in line with a decrease in BMI, (3) total energy expenditure is lower in sick elderly people given that their physical activity level, i.e. the ratio of total energy expenditure to REE, is reduced during disease averaging at 1.36, (4) energy intake (EI) being only 1.23_REE is insufficient to cover energy requirements in sick elderly patients, whereas the EI of healthy elderly people appears sufficient to cover requirements, and finally, (5) gender ceases to be a determinant of REE in people aged 60 yr or over, with the Harris & Benedict equation capable of accurately predicting mean REE in this population, whether healthy or sick.	
Evidence of polymorbidity	Some included studies described patients as polymorbid		

1660

1661

1662

1663

1664

Clinical question 5. Do protein targets higher than 1.0g/kg BW/day versus a lower target improve outcomes in polymorbid inpatients requiring nutritional support?

Recommendation 5.1

Polymorbid medical inpatients requiring nutritional support shall receive a minimum of 1.0 g of protein/kg of body weight per day in order to prevent body weight loss, reduce the risk of complications and hospital readmission and improve functional outcome

Grade of recommendation A – strong consensus (95% agreement)

16. Starke J, Schneider H, Alteheld B, Stehle P, Meier R. Short-term individual nutritional care as part of routine clinical setting improves outcome and quality of life in malnourished medical patients. <i>Clinical nutrition</i> . 2011; 2: 194-201.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
randomized controlled intervention study 1++	<p>Countries: Germany and Switzerland</p> <p>Centers:</p> <p>Setting:</p> <p>Funding Sources: grants for clinical studies and education from Nestlé and from the Exchange Organisation StudEx/Switzerland and the German Academic Exchange Service (DAAD)/Germany</p> <p>Dropout rates: 50.5 %</p> <p>Study limitations: connected to study design: Preferred outcome parameters are often influenced by other factors than nutrition alone; our study was not powered to statistically confirm a causal relation to nutrition intervention</p>	<p>Total no. patients: n = 271</p> <p>Inclusion criteria: Patients with a nutritional risk (NRS score ≥ 3)</p> <p>Exclusion criteria: no informed consent, terminal condition, expected stay <5 days (judged by physician), previous participation in this study, patient on starvation, on parenteral nutrition, and/or being on dialysis</p>	132 risk patients defined by Nutritional Risk Screening 2002, were randomized to individualized nutrition support (intervention group [n = 66]) or standard hospital care (control group [n = 66]). The present study aimed at developing and evaluating a routinely manageable concept for an improved nutritional care of malnourished in-hospital patients.
Notes	Author's Conclusion: Malnourished patients profit from nutrition support regarding nutrition status and quality of life. They have fewer complications, need fewer antibiotics and are less often re-hospitalized.		
Outcome measures/results	primary outcome measure: average daily energy and protein intake	Nutrition interventions led to higher intakes (mean [standard deviation]) in energy (1553 [341] kcal vs. 1115 [381] kcal, $p < 0.001$) and protein (65.4 [16.4] g vs. 43.9 [17.2] g, $p <$	

	<p>secondary outcome measure: Body weight, plasma vitamin levels, quality of life, complications, antibiotic therapies, readmissions and mortality, number of complications, length of hospital stay, compliance with oral nutrition standard supplement consumption</p>	<p>0.001). Intervention patients (n = 66) kept their body weight in comparison to control patients (n = 66; 0.0 [2.9] kg vs. -1.4 [3.2] kg, p = 0.008). Positive effects on plasma ascorbic acid level (46.7 [26.7] mmol/l vs. 34.1 [24.2] mmol/l, p = 0.010), SF-36 function summary scale (37 [11] % vs. 32 [9] %, p = 0.030), number of complications (4/66 vs. 13/66, p = 0.035), antibiotic therapies (1/66 vs. 8/66, p = 0.033) and readmissions (17/64 vs. 28/61, p = 0.027) were recorded.</p>
Evidence of polymorbidity	Mean number of drugs: 7 in the control group, 6 the intervention group	

17. Drommer J, Schneider H, Alteheld B, Stehle P, Meier R. Protein is an important component of nutritional support predicting complications in malnourished hospitalised patients–Details of our previous randomised controlled trial (RCT). Clinical Nutrition ESPEN. 2015;3:e124-e128.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
randomized controlled trial 1++	Setting: Funding Sources: grants from the German Academic Exchange Organisation (DAAD) and StudEx (Swiss Student Exchange Organisation) Dropout rates: 15 % Study limitations: fortification of natural food; protein as an appetite inhibitor by reducing food intake	Total no. patients: n = 118 Inclusion criteria: same as in previous trial Exclusion criteria: no informed consent, no medical patient, short hospitalization (<5 days), previous study participation, being on dialysis or parenteral nutrition.	Data of our previous randomized controlled nutritional trial was analyzed according to per protocol. Patients were randomized to either the control (CG) or intervention group (IG) according to a computer-generated randomization list and received either standard care or an individual nutritional support for 5e28 days.
Notes	Author’s Conclusion: Caloric and protein intake are important predictors of complications and the change in body weight, respectively. In contrast, age and disease severity did not influence the outcome in our nutritional trial.		
Outcome measures/results	primary outcome measure: average daily caloric and protein intake secondary outcome measure: body weight change during hospitalization, the number of hospital-acquired complications, the number of antibiotic treatments, the quality of life according to the SF-36, the length of stay (LOS) on the ward and in the hospital, the readmission rate (after 6 months) and the mortality (in the hospital and 6 months after discharge)	Repeated measure ANOVA revealed a highly significant intervention effect for both protein and caloric intake (p < 0.001) after 5 and 10 days of intervention. Patients of the intervention group (IG; n = 59) were able to keep their body weight in contrast to control group (CG; n = 59) patients (68.3 (15.5) kg vs. 64.4 (15.8) kg, p = 0.003). The mean plasma ascorbic acid level was higher in IG than in CG at discharge (47.2 (26.8) mmol/l vs. 34.1 (24.2) mmol/l, p = 0.005). The number of patients suffering from in-hospital complications was lower in IG than in CG (4/59 vs. 13/59, p = 0.034). Positive effects on the antibiotic therapies for infectious complications (1/58 vs. 8/59, p = 0.032), the SF-36 physical summary scale (37 (11) % vs. 33 (9), p = 0.039) and the readmission rates (26/54 vs. 43/58, p = 0.019) were recorded. The mean protein intake predicted the chance of having a complication whereas the body weight change was best predicted by the mean caloric intake.	
Evidence of polymorbidity	Mean number of drugs: 7 in the control group, 6 in the intervention group		

1672

1673

1674 Clinical question 7. Does disease-specific nutritional supplementation (e.g. fiber, omega 3 fatty acids, BCAA, glutamine, etc.) versus standard
1675 formulations improve outcomes in polymorbid inpatients?

1676 **Recommendation 7.1**

1677 In polymorbid medical inpatients with pressure ulcers, specific amino-acids (arginine and glutamine) and β -hydroxy β -methylbutyrate (β -HMB) can
1678 be added to oral/enteral feeds to accelerate the healing of pressure ulcers.

1679 Grade of recommendation 0 – consensus (90% agreement)

1680 **Recommendation 7.2**

1681 In polymorbid medical older inpatients requiring enteral nutrition, formulas enriched in a mixture of soluble and insoluble fibers can be used to
1682 improve bowel function

1683 Grade of recommendation 0 – strong consensus (95% agreement)

18. Wong A, Chew A, Wang C, Ong L, Zhang S, Young S. The use of a specialised amino acid mixture for pressure ulcers: a placebo-controlled trial. J Wound Care. 2014; 5.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
placebo-controlled trial 1+	Countries: Singapore Centers: Setting: acute hospital Funding Sources: Abbott Laboratories Dropout rates: 11.5 % Study limitations: to standardize a wound care regimen for all patients as the pressure ulcers were of different stages, locations and were managed differently prior to this admission, bias in interpreting data, length of time of the trial	Total no. patients: n = 26 Inclusion criteria: patients who have a hospital stay of 2 weeks and above; able to attend follow-up outpatient clinics for wound assessment; and age more than 21 years. Exclusion criteria: patients with poorly controlled diabetes (HbA1c >7.0%); on total parenteral nutrition; medically unstable upon admission to the hospital; on palliative care; admission with severe sepsis; length of stay in hospital \leq 2 weeks and unable to attend outpatient follow-ups; on fluid restriction <1L/day; requiring protein restriction; on other wound healing supplements such as vitamin C, vitamin A and zinc; presence of lower extremity ulcers with untreated peripheral vascular disease, or deep tissue infection and/or requiring debridement of necrotic/sloughy tissue; unable to tolerate oral or enteral intake >70% estimated energy requirements; and those who are unable to tolerate fluid intake 30ml/kg body weight	To compare pressure ulcer healing rates in patients supplemented with a specialized amino acid mixture containing β -hydroxy β -methylbutyrate (HMB), arginine and glutamine, and standard oral nutritional supplements versus patients supplemented with oral nutritional supplements and a placebo mixture.
Notes	Author's Conclusion: The use of specialized amino acid does not appear to reduce wound size and PUSH scores but may improve tissue viability after 2 weeks. Further confirmation on a larger scale is required to determine the benefits of supplementing additional HMB, arginine and glutamine in patients with pressure ulcers.		

Outcome measures/results	outcome measure: Anthropometry and nutritional assessment, Dietary intake assessment, Pre-albumin and C-reactive protein (CRP) levels, PU assessment included: a) onset and duration of ulcer, b) acetate tracing of wound location and wound area, c) the estimated change in proportion of viable and non-viable tissue, determined using area derived from planimetry via acetate tracings, d) wound depth and/or undermine using a sterile probe, e) wound bed and periwound appearance and f) wound exudate type and amount	There was no difference between anthropometrical measurements, biochemical parameters and nutritional intake pre- and post- study. Wound area did not decrease significantly in the short term for both groups. The proportion of viable tissues increased within 2 weeks on HMB, arginine and glutamine supplementation (p=0.02). PUSH scores showed significant improvement within 1 week of supplementation for the experimental group (p=0.013).
Evidence of polymorbidity	Confirmed by author	

1684

19. Vandewoude MF, Paridaens KM, Suy RA, Boone MA, Strobbe H. Fibre-supplemented tube feeding in the hospitalised elderly. Age Ageing. 2005; 2: 120-124.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
prospective randomized controlled trial 1++	Countries: Belgium Centers: Department of Geriatrics at the University of Antwerp Setting: Funding Sources: Dropout rates: not mentioned Study limitations: difficult to measure stool weight; use of other medication classes (anticholinergic, antidepressant and gastrokinetic agents) was too limited to draw a meaningful conclusion	Total no. patients: n = 172 Inclusion criteria: patients at the Department of Geriatrics were considered eligible for the trial when they needed enteral nutrition support Exclusion criteria: Patients with inflammatory bowel disease, liver disease (transaminases >2 x normal upper limit), renal dysfunction (creatinine >2 mg/dl), progressive malignant disease or metabolic instability	to evaluate the effect of fiber supplementation in enteral feeding on bowel function in hospitalized geriatric patients, and to assess its metabolic and nutritional efficiency an enteral nutritional regimen consisting of 30 kcal/kg in 2000 ml with a calorie/nitrogen ratio of 156 with or without fiber was instituted.
Notes	Author's Conclusion: fiber supplementation improved bowel function with reduced stool frequency and more solid stool consistency. It did not affect the nutritional efficiency of enteral feeding in hospitalized geriatric patients. Diabetes may be a risk factor for mortality in malnourished patients requiring tube feeding.		
Outcome measures/results	primary outcome measure: stool output was qualitatively evaluated by recording frequency, volume (small <1/2 cup, large >1/2 cup) and consistency (solid-formed, soft-pasty or liquid-watery). secondary outcome measure: gender, age, presence of depression and dementia, Mid-arm circumference (MAC), triceps skin-fold thickness (TSF) and arm muscle circumference (AMC), Blood parameters (blood cell count, glycaemia, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, albumin, pre-albumin, transferrin and total protein)	Overall mortality was 24% with a trend for excess mortality in diabetic patients (33.3% versus 21.6% in non-diabetics; P = 0.176). There was no difference in duration of feeding between the fiber group (27.5 days; 95% CI = 19.1–35.9) and the no fiber group (27.9 days; 95% CI = 20.2–35.5). In the fiber-supplemented group, stool frequency was lower (4.1 per week; 95% CI = 3.7–4.6) than in controls (6.3 per week; 95% CI = 5.6–6.9). Qualitatively, stool consistency was higher (P<0.001) but no difference in volume was noted. There were no differences in final laboratory parameters between groups.	
Evidence of polymorbidity	Confirmed by author		

Clinical question 8. Does early nutritional support (i.e. provided less than 48 hours post hospital admission) compared to later nutritional support improve outcomes in polymorbid inpatients?

Recommendation 8.1

Early nutritional support (i.e. provided in less than 48 hours post hospital admission) compared to later nutritional support should be performed in polymorbid medical inpatients, as sarcopenia could be decreased and self-sufficiency could be improved

Grade of recommendation: B – strong consensus (95% agreement)

20. Hegerová P, Dědková Z, Sobotka L. Early nutritional support and physiotherapy improved long-term self-sufficiency in acutely ill older patients. Nutrition. 2015; 1: 166-170.			
prospective, randomized controlled study 1++	Countries: Czech Republic Centers: Setting: Third Internal Department of Metabolic Care and Gerontology, Faculty Hospital in Hradec Králové Funding Sources: research grant PRVOUK P 37-12 Dropout rates: no dropout Study limitations:	Total no. patients: n = 200 Inclusion criteria: age >78 y, admission to the hospital as a result of acute illness, self-sufficiency of the patient before admission based on a Barthel Index (BI) score >60, and patient's consent to participate in the Study Exclusion criteria: terminal stage of disease, terminal organ failure, hospitalization in the previous 3 mo or more than two hospitalizations in the previous 6 months, indication for immediate nutritional support (recent weight loss, reduced food intake of <50% of the normal amount for more than 2 d before admission, and body mass index [BMI] <18.5 kg/m ²), low self-sufficiency before the acute disease (BI ≤ 60), advanced stage of dementia associated with loss of independence, and refusal to participate in the study	The aim of this study was to determine whether an active approach based on early nutritional therapy and exercise would influence the development of sarcopenia and impaired self-sufficiency during acute illness. The patients were randomized to a control group receiving standard treatment (n = 100) or to an intervention group (n = 100). The intervention consisted of nutritional supplements (600 kcal, 20 g/d protein) added to a standard diet and a simultaneous intensive rehabilitation program. The tolerance of supplements and their influence on spontaneous food intake, self-sufficiency, muscle strength, and body composition were evaluated during the study period. The patients were then regularly monitored for 1 y post discharge.
Notes	Author's Conclusion: The early nutritional intervention together with early rehabilitation preserves muscle mass and independence in ill older patients hospitalized because of acute disease.		
Outcome measures/results	primary outcome measure: Age, sex, diagnosis, number of hospitalization days, anthropometry, Body composition (lean tissue mass and adipose tissue), Self-sufficiency,	The provision of nutritional supplements together with early rehabilitation led to increased total energy and protein intake while the intake of standard hospital food was not reduced. The loss of lean body mass and a decrease in self-sufficiency were apparent at discharge from the hospital and 3 mo thereafter in the control group. Nutritional supplementation and	

	Nutritional risk screening (NRS)	the rehabilitation program in the study group prevented these alterations. A positive effect of nutritional intervention and exercise during the hospital stay was apparent at 6 mo post-discharge.
Evidence of polymorbidity	Confirmed by author	

21. Zheng T, Zhu X, Liang H, Huang H, Yang J, Wang S. Impact of early enteral nutrition on short term prognosis after acute stroke. Journal of Clinical Neuroscience. 2015; 9: 1473-1476.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
randomized controlled trial 1-	Countries: China Centers: Setting: Funding Sources: Dropout rates: not mentioned Study limitations:	Total no. patients: n = 146 Inclusion criteria: (1) cerebral infarction, intracranial hemorrhage or both confirmed with a CT scan or MRI within 72 hours of onset; (2) all patients who met the diagnostic standard of the Fourth National Cerebrovascular Events Conference (Chinese Neuroscience Society and Chinese Neurosurgery Society); (3) patients who might have a medical history of stroke but no apparent neurological deficit remaining prior to the onset of the current stroke; (4) focal neurological signs and dysphagia Exclusion criteria: transient ischemic attack, subarachnoid hemorrhage, severe endocrine or metabolic disorders, hematological disorders, malignancies, chronic lung and heart dysfunction, severe liver or kidney failure, stress ulcer of the digestive system, and those who died within a week of admission. Patients who received thrombolytic therapy were not included in the present study	To investigate the impact of complete enteral nutrition on Chinese patients with acute stroke, we conducted a randomized controlled trial of 146 patients with acute stroke and dysphagia, among whom 75 were supported with nasogastric nutrition and 71 received family managed nutrition after randomization.
Notes	Author’s Conclusion: Early nasogastric nutrition improves short term nutritional status and reduces complications in patients with acute stroke and dysphagia.		
Outcome measures/results	primary outcome measure: 1 Nutritional status and rate of malnutrition: calculated TSF, AMC, Hb, Alb, TG and the rate of malnutrition on the first, seventh, and twenty-first day of admission. 2 Nosocomial infection and mortality rates. 3 Neurological evaluation: National Institutes of Health Stroke Scale (NIHSS, activities of daily living Barthel index (ADLBI), and modified Rankin scale (mRS) on the first and twenty-first day of admission.	We found that the nasogastric nutrition group had a better nutritional status and reduced nosocomial infection and mortality rates after 21 days compared with patients in the family managed nutrition group. In addition, the nasogastric nutrition group showed a lower score on the NIHSS than the control group. However, the differences in the scores of the ADLBI and the 90 day mRS between the groups were not significant.	
Evidence of polymorbidity	> 2 co-occurring chronic diseases in > 50% of the study population		

Clinical question 9. Does the continued use of nutritional support after discharge compared to nutritional support during inpatient stay alone affect the outcome of polymorbid patients?

Recommendation 9.1

In malnourished polymorbid medical inpatients or those at risk of malnutrition nutritional support shall be continued after hospital discharge in order to maintain or improve body weight and nutritional status.

Grade of recommendation A – strong consensus (95% agreement)

Recommendation 9.2

In malnourished polymorbid medical inpatients or those at high risk of malnutrition, nutritional support should be continued post hospital discharge to maintain or improve functional status and quality of life.

Grade of recommendation B – strong consensus (95% agreement)

Recommendation 9.3

In polymorbid medical inpatients at high risk of malnutrition or with established malnutrition aged 65 and older, continued nutritional support post hospital discharge with either oral nutritional supplements or individualized nutritional intervention shall be considered to lower mortality.

Grade of recommendation A – strong consensus (95% agreement)

22. Gazzotti C, Arnaud-Battandier F, Parello M, Farine S, Seidel L, Albert A, Petermans J. Prevention of malnutrition in older people during and after hospitalisation: results from a randomised controlled clinical trial. Age Ageing. 2003; 3: 321-325.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
randomized controlled trial 1++	Countries: Belgium Centers: Centre Hospitalier de la Citadelle in Liège Setting: Funding Sources: not mentioned Dropout rates: 5 % Study limitations:	Total no. patients: n = 80 Inclusion criteria: aged 75 or over, admitted for acute conditions, Patients were eligible for the study only if their total MNA score ranged between 17 and 23.5 (= ‘at risk of malnutrition’) Exclusion criteria: Patients with a medical condition preventing oral feeding, end-of-life patients, patients with severe dementia (Mini Mental Score <10), patients presenting clinical signs of dehydration or heart failure, and those suffering from diseases requiring special dietary treatment (kidney or liver failure)	To prevent the occurrence of weight loss during hospitalization and following discharge by daily oral supplementation. Patients were randomized into a control group or one receiving oral supplementation. The intervention was a prescription of 200 ml sweet or salty sip feed twice daily (500 kcal, 21 g protein per day) throughout hospitalization and convalescence.
Notes	Author’s Conclusion: Use of daily oral supplementation during and after hospitalization maintains body weight and increases Mini Nutritional Assessment score in patients at risk of undernutrition.		
Outcome measures/results	primary outcome measure: MNA score, weight secondary outcome measure: Demographic and medical data recorded during the inclusion period (from day 0 to day 3), included age, sex, place of origin (home or nursing-home), reason for hospitalization and therapy, digestive side effects (bloating, nausea, diarrhea, constipation and abdominal pain)	Compliance with oral supplementation was good and daily extra energy intake was 407±184 kcal. On day 60, significant weight loss from upon admission was observed in the control group (-1.23±2.5 kg; P=0.01), but not in the supplemented group (0.28±3.8 kg; NS). At the end of the study, Mini Nutritional Assessment scores were higher in the supplemented group than in the control group (23.5±3.9 versus 20.8±3.6; P=0.01).	
Evidence of polymorbidity	Mean number of drugs: 5.8 in the control group, 5.5 in the intervention group		

23. Norman K, Kirchner H, Freudenreich M, Ockenga J, Lochs H, Pirlich M. Three month intervention with protein and energy rich supplements improve muscle function and quality of life in malnourished patients with non-neoplastic gastrointestinal disease—a randomized controlled trial. Clinical nutrition. 2008; 1: 48-56.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
randomized controlled trial 1+	Countries: Germany Centers: Charité University Medicine Berlin Setting: Funding Sources: grant from Fresenius Kabi, Bad Homburg, Germany Dropout rates: 20.8 % Study limitations: mechanisms by which ONS improve outcomes are probably multifactorial, no placebo for the nutritional supplements	Total no. patients: n = 101 Inclusion criteria: Patients classified malnourished according to the Subjective Global Assessment ¹³ (SGA B or C) suffering from a benign gastrointestinal disease Exclusion criteria: malignant disease, renal insufficiency (serum creatinine 41.3 mg/dl), life expectancy less than three months or age under 18 years, hyperhydration, implanted defibrillators, neuromuscular disease, hemiplegia or rheumatoid arthritis	We investigated the effect of a three-month post-hospital nutritional intervention with high protein and energy supplements on body composition, muscle function and quality of life (QoL) in malnourished GI patients. Eighty malnourished patients with benign digestive disease were randomized to receive either oral nutritional supplements (ONS) for three months in addition to dietary counseling (DC) (ONS patients) or only dietary counseling (DC patients).
Notes	Author's Conclusion: A three month intervention with high protein oral supplements improves outcome in malnourished patients with digestive disease in terms of functional status, QoL and rehospitalization.		
Outcome measures/results	primary outcome measure: Readmissions to hospital as a rough measure of clinical outcome) secondary outcome measure: Nutritional status (subjective global assessment), body composition (bioelectrical impedance), anthropometry, muscle function (handgrip strength and peak flow), QoL (36-item short-form questionnaire)	Age, body cell mass (BCM), muscle function, gender distribution and QoL did not differ between ONS patients (n = 38) and DC patients (n = 42) at baseline. Body weight and BCM improved significantly in both groups after three months. However, hand-grip strength (26.1±11.3–31.5±10.1 kg, p<0.0001) and peak flow (329.2±124.0–388.9±108.4 l/min, p = 0.004) improved only in the ONS patients and remained unchanged in the DC patients. Similarly, all eight scales of the QoL improved in the ONS patients compared with merely three in the DC patients. DC patients experienced significantly more readmissions (n = 20) than ONS patients (n = 10) during the study period (p = 0.041).	
Evidence of polymorbidity	Mean number of drugs: 6 in the control group, 4 in the intervention group		

24. Norman K, Pirlich M, Smoliner C, Kilbert A, Schulzke J, Ockenga J, Lochs H, Reinhold T. Cost-effectiveness of a 3-month intervention with oral nutritional supplements in disease-related malnutrition: a randomised controlled pilot study. Eur J Clin Nutr. 2011; 6: 735-742.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
randomized controlled pilot study 1+	Countries: Germany Centers: Department of Gastroenterology, Hepatology and Endocrinology, Charité University Medicine Setting: Funding Sources: grant from Fresenius Kabi, Bad Homburg, Germany Dropout rates: 28,75 % Study limitations: design of economic evaluation, only direct costs of the intervention were considered	Total no. patients: n = 160 Inclusion criteria: classified as malnourished, according to the Subjective Global Assessment (Detsky et al., 1987) (SGA B or C), and suffering from a benign gastrointestinal disease Exclusion criteria: malignant disease, renal insufficiency (serum creatinine 41.3 mg/dl), and life expectancy < 3 months or age < 18 years	Nutritional intervention with oral nutritional supplements (ONS) has been shown to increase quality of life in malnourished patients. We investigated whether post-hospital supplementation with ONS is cost-effective according to international benchmarks in malnourished patients. In total, 114 malnourished patients (50.6±16.1 years, 57 female) with benign gastrointestinal disease were included and randomized to receive either ONS for 3 months and dietary counseling at discharge (intervention, n=60) or only dietary counseling at discharge (control group, n=54).
Notes	Author's Conclusion: A 3-month intervention with ONS increases quality of life in malnourished patients. This treatment appears to be cost-effective according to international benchmarks.		
Outcome measures/results	primary outcome measure: incremental cost-effectiveness ratio (ICER) secondary outcome measure: Nutritional status, daily intake of ONS, quality of life (Short-Form (SF)-36 Health Survey) transformed into health-status utilities, Quality-adjusted life years (QALYs)	Intervention patients consumed 2.4±0.8 ONS per day. Intervention and control patients did not differ in their health status utilities at baseline (0.594±0.017 vs 0.619±0.018), but after 3 months, the health status utilities were significantly higher in intervention patients than in control patients (0.731±0.015 vs 0.671±0.016, P=0.028). Intervention was associated with significantly higher costs (ICER: €9497 and €12 099/additional QALY, respectively) but deemed cost-effective according to international thresholds (<€50 000/QALY).	
Evidence of polymorbidity	Mean number of chronic diseases and drugs: 4.6 and 3.9 in the control group, respectively; 5 and 5 in the intervention group, respectively		

25. Feldblum I, German L, Castel H, Harman-Boehm I, Shahar DR. Individualized nutritional intervention during and after hospitalization: the nutrition intervention study clinical trial. J Am Geriatr Soc. 2011; 1: 10-17.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
randomized, controlled trial 1-	Countries: Israel Centers: Internal medicine departments Setting: Funding Sources: Israel National Institute for Health Policy and Health Services Research Dropout rates: 25.8% Study limitations: high dropout rate in the nonintervention groups, results cannot be directly generalized as strict exclusion criteria were used	Total no. patients: n = 259 Inclusion criteria: hospitalized adults aged 65 and older at nutritional risk with a MNA-sf score less than 10 or those who had lost more than 10% of their weight in the previous 6 months Exclusion criteria: current diagnosis of cancer, cognitive impairment (Mini Mental State Examination (MMSE) score <23), an inability to be interviewed, language difficulties, or an unwillingness to provide informed consent	To test the hypothesis that individualized nutritional treatment during and after discharge from acute hospitalization will reduce mortality and improve nutritional outcomes. Group 1 (intervention group) received individualized nutritional treatment from a dietitian in the hospital and three home visits after discharge. Group 2 received one meeting with a dietitian in the hospital. Group 3 received standard care. Groups 2 and 3 were combined into a single group that served as the control group in the analysis.
Notes	Author's Conclusion: Lower mortality and moderate improvement in nutritional status were found in patients receiving individualized nutritional treatment during and after acute hospitalization.		
Outcome measures/results	outcome measure: Mortality, health status, nutritional outcomes, blood tests, cognition, emotional, and functional parameters	After 6 months, rise in Mini Nutritional Assessment score, adjusted for education and hospitalization ward, was significantly higher in the intervention group than in the control groups (3.01 ± 2.65 vs 1.81 ± 2.97, P=.004) mainly on the subjective assessment part (0.34 ± 0.86 vs. -0.04 ± 0.87, P=.004). The only laboratory parameter for which a difference was observed between the groups was albumin; 9.7%of the intervention group had serum albumin levels of less than 3.5 g/dL, versus 22.9% of the control group (P=.03). Mortality was significantly lower in the intervention group (3.8%) than in the control group (11.6%, P=.046).	
Evidence of polymorbidity	Mean Charlson comorbidity index: 2.5 in the control group, 2.2 in the intervention group, 2.4 in the "in-hospital" treatment group		

26. Casals C, García-Agua-Soler N, Vázquez-Sánchez M, Requena-Toro M, Padilla-Romero L, Casals-Sánchez J. Randomized clinical trial of nutritional counseling for malnourished hospital patients. Revista Clínica Española (English Edition). 2015; 6: 308-314.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
randomized clinical trial 1-	Countries: Spain Centers: Hospital Clinic Virgen de la Victoria of Malaga Setting: Funding Sources: research grant from the Government of Andalusia Dropout rates: 12.3 % Study limitations: lack of masking of the patients and health professionals	Total no. patients: Inclusion criteria: (a) hospitalization, (b) medium-high risk of malnutrition on the MUST scale, (c) older than 18 years, (d) willingness to participate in the study and signing of the informed consent form (in the event of cognitive impairment, the consent form was signed by the patient's caregiver) and (e) resident of the geographical area corresponding to the participating health center. Exclusion criteria: (a) treatment with oral food supplements, enteral or parenteral nutrition, (b) treatment with chemotherapy or radiation therapy and (c) malabsorption syndrome.	The aim of this study is to assess the impact of dietary counseling for malnourished hospital patients. In a prospective, randomized, open-label study of 106 hospital patients with malnutrition (54 in the control group and 52 in the intervention group), the intervention group received dietary counseling, and the control group underwent standard treatment.
Notes	Author's Conclusion: Nutritional counseling improved the patients' nutritional state, quality of life and degree of dependence and decreased the number of hospital readmissions.		
Outcome measures/results	outcome measure: nutritional state (body mass index, laboratory parameters, malnutrition universal screening tool), degree of dependence (Barthel index), quality of life (SF-12), degree of satisfaction (CSQ-8), the number and length of readmissions and mortality.	The patients who underwent the "intervention" increased their weight at 6 months, while the controls lost weight (difference in body mass index, 2.14 kg/m2; p < .001). The intervention group had better results when compared with the control group in the Malnutrition Universal Screening Tool scores (difference, -1.29; p < .001), Barthel index (difference, 7.49; p = .025), SF-12 (difference, 13.72; p < .001) and CSQ-8 (difference, 4.34, p < .001) and required fewer readmissions (difference, -0.37; p = .04) and shorter stays for readmissions (difference, -6.75; p = .035). Mortality and laboratory parameters were similar for the 2 groups.	
Evidence of polymorbidity	Agreement within working group, following attempt to contact author		

27. Persson M, Hytter-Landahl Å, Brismar K, Cederholm T. Nutritional supplementation and dietary advice in geriatric patients at risk of malnutrition. Clinical nutrition. 2007; 2: 216-224.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
Intervention study 1+	Countries: Sweden Centers: Department of Geriatric Medicine at Rosenlund Hospital, Stockholm Setting: Funding Sources: financial support from The Swedish Research Council (04224), Karolinska Institutet and by grants from S. Persson Family Foundation (18:35) and Sempers Foods AB. Dropout rates: 50 % Study limitations: high dropout rate due to advanced age, multiorgan disease and cognitive dysfunction, lack of placebo treatment to the control group	Total no. patients: n = 108 Inclusion criteria: not described in detail (one ward mainly treated elderly adults after trauma with or without fracture; the other ward mainly took care of acutely ill elderly patients with various somatic disorders) Exclusion criteria: not described	Effects of combined nutritional treatment of patients at risk of protein-energy malnutrition (PEM) discharged from a geriatric service were evaluated. Patients (n = 108, age 85±6 years) at risk of malnutrition according to the short form of the mini nutritional assessment were randomly allocated to dietary counseling, including liquid and multivitamin supplementation, i.e. intervention (I, n = 51) and to controls (C, n = 57).
Notes	Author's Conclusion: Combined nutritional intervention prevented weight loss and improved ADL functions in discharged geriatric patients at risk of malnutrition.		
Outcome measures/results	primary outcome measure: Body weight, biochemical indices (e.g. insulin-like growth factor I (IGF-I)), Katz activities of daily living (ADL) index, mini mental status examination (MMSE) and quality of life (QoL) by SF-36	Fifty-four patients, 29 in the I-group (86±7 years, 66% females) and 25 in the C-group (85±7 years, 72% females) completed the study according to the protocol. Both modes of analysis revealed a significant positive effect of the combined nutritional intervention on weight maintenance. Treated-as-protocol analyses showed that Katz ADL index improved in the I-group (p<0.001; p<0.05 between the groups). Serum IGF-I levels increased in the I-group (p<0.001), but were unchanged in the C-group (p = 0.07 between the groups). QoL was assessed to be low and had not changed after nutritional treatment.	
Evidence of polymorbidity	Confirmed by author		

28. Neelemaat F, Bosmans JE, Thijs A, Seidell JC. Oral nutritional support in malnourished elderly decreases functional limitations with no extra costs. Clinical nutrition. 2012; 2: 183-190.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
randomized controlled trial 1++	Countries: Netherlands Centers: University Medical Center, Amsterdam Setting: Funding Sources: The Netherlands Organisation for Health Research and Development (ZonMw) Dropout rates: 31.9 % Study limitations: follow-up period of this study was three months only, numbers of patients were not large enough to detect relevant cost differences.	Total no. patients: n = 210 Inclusion criteria: malnourished according to the following criteria: (1) Body Mass Index (BMI in kg/m2) < 20 and/or (2) >5% unintentional weight loss in the previous month and/or (3) >10% unintentional weight loss in the previous six months. Exclusion criteria: Patients, who suffered from senile dementia, could not understand the Dutch language or were not able to or willing to give informed consent.	The aim of this study was to evaluate the cost-effectiveness of nutritional supplementation from a societal perspective Patients in the intervention group received nutritional supplementation (energy and protein enriched diet, oral nutritional support, calcium-vitamin D supplement, telephone counseling by a dietician) until three months after discharge from hospital. Patients in the control group received usual care (control).
Notes	Author's Conclusion: A multi-component nutritional intervention to malnourished elderly patients for three months after hospital discharge leads to significant improvement in functional limitations and is neutral in costs. A follow-up of three months is probably too short to detect changes in QALYs or physical activities.		
Outcome measures/results	primary outcome measure: Quality Adjusted Life Years (QALYs), physical activities and functional limitations secondary outcome measure: Incremental cost-effectiveness ratios	210 patients were included, 105 in each group. After three months, no statistically significant differences in quality of life and physical activities were observed between groups. Functional limitations decreased significantly more in the intervention group (mean difference -0.72, 95% CI-1.15; -0.28). There were no differences in costs between groups. Cost-effectiveness for QALYs and physical activities could not be demonstrated. For functional limitations we found a 0.95 probability that the intervention is cost effective in comparison with usual care for ceiling ratios >€6,500.	
Evidence of polymorbidity	Confirmed by author		

29. Neelemaat F, Bosmans JE, Thijs A, Seidell JC. Post-discharge nutritional support in malnourished elderly individuals improves functional limitations. Journal of the American Medical Directors Association. 2011; 4: 295-301.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
randomized controlled trial 1++	Countries: Netherlands Centers: University Medical Center, Amsterdam Setting: Funding Sources: The Netherlands Organisation for Health Research and Development (ZonMw) Dropout rates: 31.9 % Study limitations: a follow-up of only 3 months	Total no. patients: n = 210 Inclusion criteria: malnourished according to the following criteria: (1) Body Mass Index (BMI in kg/m2) < 20 and/or (2) >5% unintentional weight loss in the previous month and/or (3) >10% unintentional weight loss in the previous six months. Exclusion criteria: Patients, who suffered from senile dementia, could not understand the Dutch language or were not able to or willing to give informed consent.	Hospital-admitted malnourished elderly patients (\$60 years) were randomized to receive either nutritional supplementation (energy and protein enriched diet, oral nutritional support, calcium, vitamin D supplement, telephone counseling by a dietitian) for 3 months post discharge or usual care.
Notes	Author’s Conclusion: Three months of oral nutritional support to malnourished elderly decreased functional limitations and increased body weight. It can be questioned if a follow-up of only 3 months was not too short to detect differences on physical performance and physical activities as well.		
Outcome measures/results	primary outcome measure: functional limitations, physical performance, physical activities, body weight, fat free mass, and handgrip strength secondary outcome measure:	Body weight increased more in the intervention group than in the control group; this was significant for the highest body weight category (mean difference 3.4 kg, 95% CI 0.2–6.6). Functional limitations decreased more (mean difference –0.5 (95% CI –1.0–0.1) in the intervention group than in the control group. When excluding patients who had already received nutritional support before the start of the study, this reached significance. No significant differences could be demonstrated for physical performance, physical activities, fat-free mass, or handgrip strength.	
Evidence of polymorbidity		Confirmed by author	

30. Neelemaat F, Lips P, Bosmans JE, Thijs A, Seidell JC. Short-term oral nutritional intervention with protein and vitamin D decreases falls in malnourished older adults. J Am Geriatr Soc. 2012; 4: 691-699.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
randomized controlled trial 1++	Countries: Netherlands Centers: University Medical Center, Amsterdam Setting: Funding Sources: The Netherlands Organization for Health Research and Development (ZonMw) Dropout rates: 28.6 % Study limitations: not blinded, method of collection of nutrition data was not optimal, loss to follow-up was 30%	Total no. patients: n = 210 Inclusion criteria: All older adults (aged ≥ 60) newly admitted (expected length of hospital stay > 2 days) to an acute hospital who are malnourished according to the following criteria: body mass index (BMI) of 20.0 kg/m2 or less, 5% or more self-reported unintentional weight loss in the previous month, or 10% or more self-reported unintentional weight loss in the previous 6 months Exclusion criteria: Individuals with dementia	To evaluate the effects of a short-term nutritional intervention with protein and vitamin D on falls in malnourished older adults, participants were randomized to receive nutritional intervention (energy- and protein enriched diet, oral nutritional supplements, calcium, vitamin D supplement, telephone counseling by a dietitian) for 3 months after discharge or usual care.
Notes	Author's Conclusion: short-term nutritional intervention consisting of oral nutritional supplements and calcium and vitamin D supplementation and supported by dietetic counseling in malnourished older adults decreases the number of patients who fall and fall incidents.		
Outcome measures/results	Primary outcome measure: Number of participants who fell, fall incidents, serum 25-hydroxyvitamin D, and dietary intake. Secondary outcome measure: Fat-Free Mass, Hand Grip Strength, Physical Activities, Functional Limitations, and Physical Performance	Three months after discharge, 10 participants (10%) in the intervention group had fallen at least once, compared with 24 (23%) in the control group (hazard ratio = 0.41, 95% confidence interval (CI) = 0.19–0.86). There were 57 fall incidents (16 in the intervention group; 41 in the control group). A significantly higher intake of energy (280 kcal, 95% CI = 37–524 kcal) and protein (11 g, 95% CI = 1–25 g) and significantly higher serum 25-hydroxyvitamin D levels (10.9 nmol/L, 95% CI = 2.9–18.9 nmol/L) were found in participants in the intervention group than in controls.	
Evidence of polymorbidity	Confirmed by author		

31. Deutz NE, Matheson EM, Matarese LE, Luo M, Baggs GE, Nelson JL, Hegazi RA, Tappenden KA, Ziegler TR, NOURISH Study Group. Readmission and mortality in malnourished, older, hospitalized adults treated with a specialized oral nutritional supplement: a randomized clinical trial. Clinical Nutrition. 2016;1:18-26.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
Multicenter, randomized, placebo-controlled, double-blind trial 1++	Countries: USA Centers: Setting: Funding Sources: Abbott Nutrition Dropout rates: 4.9 % Study limitations: Limited generalizability; patients represent a selected hospitalized population.	Total no. patients: n = 652 Inclusion criteria: aged ≥ 65 years with a recent hospital admission (within 72 h) with a primary diagnosis of CHF, AMI, PNA, or COPD. Patients were required to have a Subjective Global Assessment (SGA) class of B (moderate or suspected malnutrition) or C (severe malnutrition) Exclusion criteria: diabetes mellitus (type 1 or 2) due to product composition not intended for patients with diabetes mellitus; current active or treated cancer, and impaired renal or liver function	Evaluation of a high-protein oral nutritional supplement (HP-HMB) containing beta-hydroxybeta-methylbutyrate on post discharge outcomes of non elective readmission and mortality in malnourished, hospitalized older adults. Standard-of-care plus HP-HMB (n = 328) or a placebo supplement (n = 324), 2 servings/day.
Notes	Author's Conclusion: Although no effects were observed for the primary composite endpoint, compared with placebo HP-HMB decreased mortality and improved indices of nutritional status during the 90-day observation period.		
Outcome measures/results	primary outcome measure: 90-day post discharge incidence of death or non-elective readmission secondary outcome measure: 30- and 60-day post-discharge incidence of death or readmission, length of stay (LOS), SGA class, body weight, and activities of daily living (ADL)	The primary composite endpoint was similar between HP-HMB (26.8%) and placebo (31.1%). No between-group differences were observed for 90-day readmission rate, but 90-day mortality was significantly lower with HP-HMB relative to placebo (4.8% vs. 9.7%; relative risk 0.49, 95% confidence interval [CI], 0.27 to 0.90; p = 0.018). The number-needed-to-treat to prevent 1 death was 20.3 (95% CI: 10.9, 121.4). Compared with placebo, HP-HMB resulted in improved odds of better nutritional status (SGA class, OR, 2.04, 95% CI: 1.28, 3.25, p = 0.009) at day 90, and an increase in body weight at day 30 (p = 0.035). LOS and ADL were similar between treatments.	
Evidence of polymorbidity	Mean Charlson comorbidity index: 2.05 in the control group, 2.12 in the intervention group.		

1708

1709

1710

1711

Clinical question 10. Does the monitoring of physical functions, when it is possible, compared to monitoring of nutritional parameters (e.g. body weight, energy and protein intakes) improve other outcomes in polymorbid inpatients receiving nutritional support?

Recommendation 10.1:

Nutritional parameters should be monitored to assess responses to nutritional support, while functional indices should be used to assess other clinical outcomes (i.e., survival, quality of life) in polymorbid medical inpatients.

Grade of recommendation B – strong consensus (95% agreement)

32. Mendenhall CL, Moritz TE, Roselle GA, Morgan TR, Nemchausky BA, Tamburro CH, Schiff ER, McClain CJ, Marsano LS, Allen JI. Protein energy malnutrition in severe alcoholic hepatitis: diagnosis and response to treatment. J Parenter Enteral Nutr. 1995; 4: 258-265.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
Intervention study 2+	<p>Countries:</p> <p>Centers: eight Department of Veterans Affairs (DVA) Medical Centers.</p> <p>Setting:</p> <p>Funding Sources: Cooperative Studies Program of the Department of Veterans Affairs Medical Research Service.</p> <p>Dropout rates: no dropout</p> <p>Study limitations:</p>	<p>Total no. patients: n = 271</p> <p>Inclusion criteria: Male patients with a clinical diagnosis of alcoholic hepatitis (AH), histologic confirmation of the etiology of the liver disease was not an absolute requirement so that severely ill patients with coagulopathy could be enrolled.</p> <p>Exclusion criteria: not mentioned</p>	Protein energy malnutrition (PEM) was evaluated and expressed as percent of low normal in 271 patients initially, at 1 month and at 3 months. Active therapy consisted of anabolic steroid oxandrolone (OX) plus a high caloric food supplement vs a matching placebo and a low calorie supplement.
Notes	<p>Author's Conclusion: Deterioration in nutritional parameters is a significant risk factor for survival in severe patients with alcoholic hepatitis. This deterioration is reversible with standard hospital care. Active therapy further improves creatinine height index, mid arm muscle area and total lymphocyte counts. Hence, these later parameters appear to be the best indicators for follow-up assessments.</p>		
Outcome measures/results	<p>outcome measure: Nutritional status, grip strength, immune status</p>	<p>Most of the parameters improved significantly from baseline on standard care; the largest improvement seen in visceral proteins, the smallest in fat stores (skinfold thickness). Total PEM score significantly correlated with 6 month mortality (p=0.0012). Using logistic regression analysis, creatinine height index, hand grip strength and total peripheral blood lymphocytes were the best risk factors for survival. When CD lymphocyte subsets replaced total lymphocyte counts in the equation, CD8 levels became a significant risk factor (p=.004). Active treatment produced significant improvements in those parameters related to total body and muscle mass (i.e., mid arm muscle area, p=0.02; creatinine height index, p=0.03; percent ideal body weight,</p>	

		p=0.04).
Evidence of polymorbidity	> 2 co-occurring chronic diseases in > 50% of the study population	

33. Norman K, Kirchner H, Freudenreich M, Ockenga J, Lochs H, Pirlich M. Three month intervention with protein and energy rich supplements improve muscle function and quality of life in malnourished patients with non-neoplastic gastrointestinal disease—a randomized controlled trial. Clinical nutrition. 2008; 1: 48-56.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
randomized controlled trial 1+	Countries: Germany Centers: Charité University Medicine Berlin Setting: Funding Sources: grant from Fresenius Kabi, Bad Homburg, Germany Dropout rates: 20.8 % Study limitations: mechanisms by which ONS improve outcomes are probably multifactorial, no placebo for the nutritional supplements	Total no. patients: n = 101 Inclusion criteria: Patients classified malnourished according to the Subjective Global Assessment ¹³ (SGA B or C) suffering from a benign gastrointestinal disease Exclusion criteria: malignant disease, renal insufficiency (serum creatinine 41.3 mg/dl), life expectancy less than three months or age under 18 years, Hyperhydration, implanted defibrillators, neuromuscular disease, hemiplegia or rheumatoid arthritis	We investigated the effect of a three-month post-hospital nutritional intervention with high protein and energy supplements on body composition, muscle function and quality of life (QoL) in malnourished GI patients. Eighty malnourished patients with benign digestive disease were randomized to receive either oral nutritional supplements (ONS) for three months in addition to dietary counseling (DC) (ONS patients) or only dietary counseling (DC patients).
Notes	Author's Conclusion: A three month intervention with high protein oral supplements improves outcome in malnourished patients with digestive disease in terms of functional status, QoL and rehospitalization.		
Outcome measures/results	primary outcome measure: Readmissions to hospital as a rough measure of clinical outcome) secondary outcome measure: Nutritional status (subjective global assessment), body composition (bioelectrical impedance), anthropometry, muscle function (handgrip strength and peak flow), QoL (36-item short-form questionnaire)	Age, body cell mass (BCM), muscle function, gender distribution and QoL did not differ between ONS patients (n = 38) and DC patients (n = 42) at baseline. Body weight and BCM improved significantly in both groups after three months. However, hand-grip strength (26.1±11.3–31.5±10.1 kg, p<0.0001) and peak flow (329.2±124.0–388.9±108.4 l/min, p = 0.004) improved only in the ONS patients and remained unchanged in the DC patients. Similarly, all eight scales of the QoL improved in the ONS patients compared with merely three in the DC patients. DC patients experienced significantly more readmissions (n = 20) than ONS patients (n = 10) during the study period (p = 0.041).	
Evidence of polymorbidity	Mean number of drugs: 6 in the control group, 4 in the intervention group		

1719

1720

Clinical question 11. Does meeting more than 75% of energy and/or protein requirements (as an indicator of compliance) versus a lower percentage improve outcomes in polymorbid inpatients receiving nutritional support?

Recommendation 11.1:

In polymorbid medical inpatients with reduced food intake and hampered nutritional status at least 75% of calculated energy and protein requirements should be achieved in order to reduce the risk of adverse outcomes

Grade of recommendation B – strong consensus (100% agreement)

Recommendation 11.2:

Energy and protein fortified foods can be used in order to reach those relevant energy and protein targets in polymorbid medical inpatients

Grade of recommendation 0 – strong consensus (100% agreement)

34. Sullivan DH, Sun S, Walls RC. Protein-energy undernutrition among elderly hospitalized patients: a prospective study. JAMA. 1999; 21: 2013-2019.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
Prospective cohort study 2++	<p>Countries:</p> <p>Centers: University-affiliated Department of Veterans Affairs hospital</p> <p>Setting:</p> <p>Funding Sources: with an observational study we cannot determine whether poor nutrient intake caused increased in-hospital and 90-day mortality</p> <p>Dropout rates: 28 %</p> <p>Study limitations: with an observational study we cannot determine whether poor nutrient intake caused increased in-hospital and 90-day mortality</p>	<p>Total no. patients: n = 691</p> <p>Inclusion criteria: patients 65 years or older admitted to a general medical or surgical ward</p> <p>Exclusion criteria: Patients with metastatic cancer and those receiving palliative care for other terminal conditions, patients with a length of stay of fewer than 4 days</p>	To identify the distribution of average daily nutrient intake among the non-terminally ill hospitalized elderly, ascertain what factors contribute to persistently low intakes, and determine whether the adequacy of nutrient intake correlates with the risk of mortality.
Notes	<p>Author's Conclusion: Throughout their hospitalization, many elderly patients were maintained on nutrient intakes far less than their estimated maintenance energy requirements, which may contribute to an increased risk of mortality. Given the difficulties reversing established nutritional deficits in the elderly, greater efforts should be made to prevent the development of such deficits during hospitalization.</p>		

Outcome measures/results	<p>primary outcome measure: daily in-hospital nutrient intake</p> <p>secondary outcome measure: Admission illness severity, average length of stay, and admission albumin and prealbumin levels</p>	<p>A total of 102 patients (21%) had an average daily in-hospital nutrient intake of less than 50% of their calculated maintenance energy requirements. Admission illness severity, average length of stay, and admission albumin and prealbumin levels for this low nutrient group did not differ significantly from those of the remaining patients. However, the low nutrient group had lower mean (SD) discharge serum total cholesterol (154 [44] mg/dL [4 [1.1] mmol/L] vs 173 [42] mg/dL [4.5 [1.1] mmol/L]; $P=.001$), albumin (29.1 [6.7] vs 33.2 [6.1] g/L, $P=.001$), and prealbumin (162 [69] vs 205 [68] mg/L; $P=.001$) concentrations and a higher rate of in-hospital mortality (relative risk, 8.0; 95% confidence interval, 2.8-22.6) and 90-day mortality (relative risk, 2.9; 95% confidence interval, 1.4-6.1). Contributing to the problem of inadequate nutrient intake, patients were frequently ordered to have nothing by mouth and were not fed by another route. Neither canned supplements nor nutritional support were used effectively.</p>
Evidence of polymorbidity	Confirmed by author	

35. Munk T, Beck A, Holst M, Rosenbom E, Rasmussen H, Nielsen M, Thomsen T. Positive effect of protein-supplemented hospital food on protein intake in patients at nutritional risk: a randomised controlled trial. Journal of Human Nutrition and Dietetics. 2014; 2: 122-132.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
randomized controlled trial 1+	Countries: Denmark Centers: Departments of Oncology, Orthopaedics and Urology, University Hospital, Herlev, Denmark Setting: Funding Sources: Herlev University Hospital Research Unit, 'Toft Care System' (protein powder used free of charge) Dropout rates: 4 % Study limitations: no blinding of ward staff and data assessors	Total no. patients: n = 84 Inclusion criteria: <ul style="list-style-type: none">• newly-admitted patients ≥18 years old who were at nutritional risk according to the validated Nutritional Risk Screening-2002 (NRS-2002) tool (≥3)• patients who were able to eat orally,• an anticipated length of hospitalization of ≥3 days,• sufficient language proficiency. Exclusion criteria: <ul style="list-style-type: none">• dysphagia,• food allergy or intolerance,• anatomical obstructions preventing oral food intake,• patients who exclusively received enteral or parenteral nutrition,• terminal patients.	A single-blinded randomized controlled trial was conducted. Eighty-four participants at nutritional risk, recruited from the departments of Oncology, Orthopedics and Urology, were included. The intervention group (IG) received the protein-supplemented food service concept. The control group (CG) received the standard hospital menu. Primary outcome comprised the number of patients achieving ≥75% of energy and protein requirements. Secondary outcomes comprised mean energy and protein intake, body weight, handgrip strength and length of hospital stay.
Notes	Author's Conclusion: The novel food service concept had a significant positive impact on overall protein intake and on weight-adjusted energy intake in hospitalized patients at nutritional risk.		
Outcome measures/results	primary outcome measure: number of patients achieving ≥75% of energy and protein requirements secondary outcome measure: mean energy and protein intake, body weight, handgrip strength and length of hospital stay.	In IG, 76% versus 70% CG patients reached ≥75% of their energy requirements (P = 0.57); 66% IG versus 30% CG patients reached ≥75% of their protein requirements (P = 0.001). The risk ratio for achieving ≥75% of protein requirements: 2.2 (95% confidence interval = 1.3–3.7); number needed to treat = 3 (95% confidence interval = 2–6). IG had a higher mean intake of energy and protein when adjusted for body weight (CG: 82 kJ kg ⁻¹ versus IG: 103 kJ kg ⁻¹ , P = 0.013; CG: 0.7 g protein kg ⁻¹ versus 0.9 g protein kg ⁻¹ , P = 0.003). Body weight, handgrip strength and length of hospital stay did not differ between groups.	
Evidence of polymorbidity	Agreement within working group, following attempt to contact author		

1732

1733

1734

1735 **Clinical question 12. Do organizational changes in nutritional support (e.g. intervention of a steering committee, implementation of protected**
 1736 **mealtimes, different budget allocation) versus no changes improve outcomes of polymorbid inpatients?**

1737

1738 **Recommendation 12.1:**

1739 **Organizational changes in nutritional support provision should be implemented for polymorbid medical inpatients who are malnourished or at risk**
 1740 **of malnutrition. In particular, interventions that ensure the provision of fortified menus for at-risk patients, establishing a nutrition support team**
 1741 **and the use of multi-disciplinary nutrition protocols should be implemented**

1742 **Grade of recommendation B – strong consensus (100% agreement)**

1743

36. Kennedy JF, Nightingale JM. Cost savings of an adult hospital nutrition support team. Nutrition. 2005; 11: 1127-1133.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
Applied nutritional investigation 2+	Countries: United Kingdom Centers: university hospital Leicester Royal Infirmary Setting: Funding Sources: - Dropout rates: - Study limitations: clear cost savings have not yet been Reported as ongoing costs of bed occupancy and staff time are not included	Total no. patients: pre-NST: n = 54 NST: n= 133 Inclusion criteria: no formal process for selecting patients for PN Exclusion criteria: -	Hospital-based nutrition support team (NST) may need to demonstrate cost savings and quality benefits. The primary aim of this study was to determine whether an NST could show tangible cost savings (equipment, investigations, and medication costs) from managing patients considered for parenteral nutrition (PN). Secondary aims related to the quality issues of placement of PN catheters, catheter- related sepsis (CRS), duration of parenteral nutrition, and mortality. An NST was formed in 1999 and worked in all adult areas of a university hospital (Leicester Royal Infirmary). Comparative data about all patients given PN were collected for 2 consecutive years (a retrospective pre-NST year and a prospective NST year).

Notes	Author's Conclusion: Although the number of PN days increased with an NST, tangible cost savings of £50 715 were demonstrated within the NST year by avoided PN episodes and a decreased incidence of CRS. These savings justify the salaries of a nutrition nurse specialist and a senior dietitian.
Outcome measures/results	<p>primary outcome measure: Tangible cost saving</p> <p>secondary outcome measure: diagnosis, reasons for PN, Duration of PN, complications (especially CRS), days of feeding, Mortality,</p> <p>In the pre-NST year there were 82 PN episodes (54 patients), 665 PN days, and a CRS rate of 71% (seven infections/100 PN days). In the NST year, there were 133 referrals for PN but only 78 PN episodes (75 patients, 59% of referrals), 752 PN days, and a decreased overall CRS rate of 29% (three infections/100 PN days, $P < 0.05$) but a rate of 7% (0.6 infection/100 PN days) in the final 3 months of the NST year. Tangible cost savings for the NST year were derived from 55 avoided PN episodes (£42 741) and 35 avoided CRS episodes (£7974). Thirty-nine percent of PN catheters were inserted by the NST with no insertion-related complications. Competency-based training of ward nursing staff decreased the CRS rate. Mean duration of PN increased from 8 to 10 d (P not significant). In-hospital mortality for patients who had PN was 23 of 54 (43%) in the pre-NST year compared with 18 of 75 (24%) in the NST year ($P < 0.05$).</p>

37. Munk T, Beck A, Holst M, Rosenbom E, Rasmussen H, Nielsen M, Thomsen T. Positive effect of protein-supplemented hospital food on protein intake in patients at nutritional risk: a randomised controlled trial. Journal of Human Nutrition and Dietetics. 2014; 2: 122-132.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
randomized controlled trial 1+	Countries: Denmark Centers: Departments of Oncology, Orthopaedics and Urology, University Hospital, Herlev, Denmark Setting: Funding Sources: Herlev University Hospital Research Unit, 'Toft Care System' (protein powder used free of charge) Dropout rates: 4 % Study limitations: no blinding of ward staff and data assessors	Total no. patients: n = 84 Inclusion criteria: • newly-admitted patients ≥18 years old who were at nutritional risk according to the validated Nutritional Risk Screening-2002 (NRS-2002) tool (≥3) • patients who were able to eat orally, • an anticipated length of hospitalization of ≥3 days, • sufficient language proficiency. Exclusion criteria: • dysphagia, • food allergy or intolerance, • anatomical obstructions preventing oral food intake, • patients who exclusively received enteral or parenteral nutrition, • terminal patients.	A single-blinded randomized controlled trial was conducted. Eighty-four participants at nutritional risk, recruited from the departments of Oncology, Orthopedics and Urology, were included. The intervention group (IG) received the protein-supplemented food service concept. The control group (CG) received the standard hospital menu. Primary outcome comprised the number of patients achieving ≥75% of energy and protein requirements. Secondary outcomes comprised mean energy and protein intake, body weight, handgrip strength and length of hospital stay.
Notes	Author's Conclusion: The novel food service concept had a significant positive impact on overall protein intake and on weight-adjusted energy intake in hospitalized patients at nutritional risk.		
Outcome measures/results	primary outcome measure: number of patients achieving ≥75% of energy and protein requirements secondary outcome measure: mean energy and protein intake, body weight, handgrip strength and length of hospital stay.	In IG, 76% versus 70% CG patients reached ≥75% of their energy requirements (P = 0.57); 66% IG versus 30% CG patients reached ≥75% of their protein requirements (P = 0.001). The risk ratio for achieving ≥75% of protein requirements: 2.2 (95% confidence interval = 1.3–3.7); number needed to treat = 3 (95% confidence interval = 2–6). IG had a higher mean intake of energy and protein when adjusted for body weight (CG: 82 kJ kg ⁻¹ versus IG: 103 kJ kg ⁻¹ , P = 0.013; CG: 0.7 g protein kg ⁻¹ versus 0.9 g protein kg ⁻¹ , P = 0.003). Body weight, handgrip strength and length of hospital stay did not differ between groups.	
Evidence of polymorbidity	Agreement within working group, following attempt to contact author		

38. Rypkema G, Adang E, Dicke H, Naber T, De Swart B, Disselhorst L, Goluke-Willemse G, Rikkert MO. Cost-effectiveness of an interdisciplinary intervention in geriatric inpatients to prevent malnutrition. Journal of Nutrition Health and Aging. 2004; 2: 122-127.			
Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
prospective, controlled study 2+	<p>Countries: Netherlands</p> <p>Centers: The inpatient geriatric service of a university hospital (UMC Nijmegen) and a geriatric ward of a non-academic teaching hospital (Rijnstate Hospital, Arnhem)</p> <p>Setting:</p> <p>Funding Sources: research grant from the joint society of Dutch Universities (VAZ) and partly by Nutricia, Inc.</p> <p>Dropout rates:</p> <p>Study limitations: Missing data might have been caused by selection bias, intervention and control group were located in two separate geriatric units in two different hospitals</p>	<p>Total no. patients: n = 298</p> <p>Inclusion criteria: All patients admitted to the geriatrics units (aged over 60 years) during a 10 month period in the year 2001 who were non-terminally ill and admitted for more than two days were eligible for inclusion</p> <p>Exclusion criteria: Patients admitted for over 150 days (and waiting for institutional care) were excluded from the study.</p>	In order to reduce protein-energy malnutrition in older people during hospitalization, an early interdisciplinary intervention is needed. We developed a protocol which includes screening for malnutrition, dysphagia and dehydration on admission, followed by immediate interventions. One of the geriatric wards applied the protocol (N=140) while the other provided standard care (N=158).
Notes	Author's Conclusion: An early interdisciplinary intervention approach can be effective in reducing protein-energy malnutrition and related hospital-acquired infections and appears to be economically feasible.		
Outcome measures/results	<p>primary outcome measure: Weight, Body Mass Index (BMI), Barthel Index, MNA-sf, date of birth and sex, Nosocomial infections, pressure score, length of stay, Edema, heart failure</p>	There was a 0.8 kg loss (SEM 0.3 kg) in average weight in the standard care group and a 0.9 kg gain (SEM 0.2 kg) in the intervention group (p<0.001). The number of hospital acquired infections was significantly lower in the intervention group (33/140 versus 58/158, p=0.01) but no significant difference in number of patients with pressure sores (23/140 versus 33/158) was found. Costs were not significantly different: 7516 versus 7908 Euro/patient for intervention versus controls, respectively	
Evidence of polymorbidity	Agreement within working group, following attempt to contact author		

1744
1745
1746

Appendix 3 - Supplementary data: summary of clinical questions and recommendations

Topic	Clinical question and recommendation(s)/ statement(s)
Indication	<p>1. Does nutritional support based on screening and/or assessment versus no screening and/or assessment improve outcomes in polymorbid inpatients?</p> <p><i>Recommendation 1.1</i> <i>In polymorbid medical inpatients, a quick and simple nutritional screening method using different validated tools should be applied to identify malnutrition risk. In patients at risk, a more detailed assessment should be performed and a treatment plan should be developed, to consent an early adequate nutritional therapy and to define quality outcome measures of success.</i> <i>(Grade of recommendation B) - strong consensus (100% agreement)</i></p>
Route of feeding	<p>2. In polymorbid inpatients whose nutritional requirements can be met orally, does the use of oral nutritional supplements (ONS), with or without nutritional counseling, versus no ONS, improve outcomes?</p> <p><i>Recommendation 2.1</i> <i>In malnourished polymorbid medical inpatients or those at high risk of malnutrition who can safely reach their nutritional requirements orally, ONS high in energy and protein shall be considered to improve their nutritional status and quality of life.</i> <i>(Grade of recommendation A) - strong consensus (95% agreement)</i></p> <p><i>Recommendation 2.2</i> <i>In malnourished polymorbid medical inpatients or those at high risk of malnutrition, nutrient-specific ONS should be administered, when they may maintain muscle mass, reduce mortality or improve quality of life.</i> <i>(Grade of recommendation B) - consensus (89% agreement)</i></p> <p><i>Recommendation 2.3</i> <i>In polymorbid medical inpatients who are malnourished or at high risk of malnutrition and can safely reach their nutritional requirements orally, ONS should be considered as a cost-effective way of intervention towards improved outcomes.</i> <i>(Grade of recommendation B) - strong consensus (95% agreement)</i></p>
	<p>3. In patients where nutritional requirements cannot be met orally, does the use of enteral nutrition (EN) compared to parenteral nutrition (PN) (total or supplemental) result in improved outcomes in polymorbid inpatients?</p> <p><i>Recommendation 3.1</i> <i>In polymorbid medical inpatients whose nutritional requirements cannot be met orally, EN can be administered. In these cases, the use of EN may be superior to PN because of a lower risk of infectious and non-infectious complications.</i> <i>(Grade of recommendation 0) - strong consensus (100% agreement)</i></p>
Energy requirements	<p>4. Does the estimation of energy requirements with a prediction equation versus a weight-based formula improve outcomes of polymorbid inpatients requiring nutritional support?</p> <p><i>Recommendation 4.1</i></p>

*Energy requirements in polymorbid medical inpatients can be estimated using indirect calorimetry (IC), a published prediction equation or a weight-based formula.
(Grade of recommendation 0) - strong consensus (96% agreement)*

Recommendation 4.2

*In the absence of IC, total energy expenditure (TEE) for polymorbid older patients (aged > 65 years) can be estimated using the formula 27 kcal/kg actual body weight. Resting energy expenditure (REE) can be estimated using the formula 18 - 20 kcal/kg body weight with the addition of activity or stress factors to estimate TEE.
(Grade of recommendation 0) – strong consensus (95% agreement)*

Recommendation 4.3.a

*In the absence of IC, REE for severely underweight patients can be estimated using the formula 30 kcal/kg body weight.
(Grade of recommendation 0) - consensus (89% agreement)*

Recommendation 4.3.b

*This target of 30 kcal/kg body weight in severely underweight patients should be cautiously and slowly achieved, as this is a population at high risk of refeeding syndrome.
(Grade of recommendation GPP) - strong consensus (100% agreement)*

5. Do protein targets higher than 1.0g/kg BW/day versus a lower target improve outcomes in polymorbid inpatients requiring nutritional support?

Protein
requirements

Recommendation 5.1

*Polymorbid medical inpatients requiring nutritional support shall receive a minimum of 1.0 g of protein/kg of body weight per day in order to prevent body weight loss, reduce the risk of complications and hospital readmission and improve functional outcome.
(Grade of recommendation A) - strong consensus (95% agreement)*

6. In patients exclusively fed orally, does the supplementation of micronutrients (vitamins and trace elements) compared to no supplements improve outcomes in polymorbid inpatients?

Micronutrients
requirements

Recommendation 6.1.

*In polymorbid medical inpatients exclusively fed orally adequate intake of micronutrients (vitamins and trace elements) to meet daily estimated requirements should be ensured.
(Grade of recommendation GPP) - strong consensus (100% agreement)*

Recommendation 6.2.

*Polymorbid medical inpatients exclusively fed orally with documented or suspected micronutrient deficiencies should be repleted.
(Grade of recommendation GPP) - strong consensus (93% agreement)*

7. Does disease-specific nutritional supplementation (e.g. fibre, omega 3 fatty acids, BCAA, glutamine, etc.) versus standard formulations improve outcomes in polymorbid inpatients?

Disease-
specific
nutrients

Recommendation 7.1

*In polymorbid medical inpatients with pressure ulcers, specific amino-acids (arginine and glutamine) and β -hydroxy β -methylbutyrate (β HMB) can be added to oral/enteral feeds to accelerate the healing of pressure ulcers.
(Grade of recommendation 0) - consensus (90 % agreement)*

Recommendation 7.2

In polymorbid medical older inpatients requiring enteral nutrition, formulas enriched in a

*mixture of soluble and insoluble fibers can be used to improve bowel function.
(Grade of recommendation 0) - strong consensus (95% agreement)*

8. Does early nutritional support (i.e. provided less than 48h post hospital admission) compared to later nutritional support improve outcomes in polymorbid inpatients?

Recommendation 8.1

*Early nutritional support (i.e. provided in less than 48 hours post hospital admission) compared to later nutritional support should be performed in polymorbid medical inpatients, as sarcopenia could be decreased and self-sufficiency could be improved
(Grade of recommendation B) - strong consensus (95% agreement)*

9. Does the continued use of nutritional support after discharge compared to nutritional support during inpatient stay alone affect the outcomes of polymorbid inpatients?

Timing

Recommendation 9.1

*In malnourished polymorbid medical inpatients or those at risk of malnutrition nutritional support shall be continued after hospital discharge in order to maintain or improve body weight and nutritional status.
(Grade of recommendation A) - strong consensus (95% agreement)*

Recommendation 9.2

*In malnourished polymorbid medical inpatients or those at high risk of malnutrition, nutritional support should be continued post hospital discharge to maintain or improve functional status and quality of life.
(Grade of recommendation B) - strong consensus (95% agreement)*

Recommendation 9.3

*In polymorbid medical inpatients at high risk of malnutrition or with established malnutrition aged 65 and older, continued nutritional support post hospital discharge with either ONS or individualized nutritional intervention shall be considered to lower mortality.
(Grade of recommendation A) - strong consensus (95% agreement)*

10. Does the monitoring of physical functions, when it is possible, compared to monitoring of nutritional parameters (e.g. body weight, energy and protein intakes) improve other outcomes in polymorbid inpatients receiving nutritional support?

Monitoring

Recommendation 10.1

*Nutritional parameters should be monitored to assess responses to nutritional support, while functional indices should be used to assess other clinical outcomes (i.e., survival, quality of life) in polymorbid medical inpatients.
(Grade of recommendation B) - strong consensus (95% agreement)*

11. Does meeting more than 75% of energy and/or protein requirements (as an indicator of compliance) versus a lower percentage improve outcomes in polymorbid inpatients receiving nutritional support?

Recommendation 11.1

*In polymorbid medical inpatients with reduced food intake and hampered nutritional status at least 75% of calculated energy and protein requirements should be achieved in order to reduce the risk of adverse outcomes.
(Grade of recommendation B) - strong consensus (100% agreement)*

Recommendation 11.2

Energy and protein fortified foods can be used in order to reach those relevant energy and protein targets in polymorbid medical inpatients.

(Grade of recommendation 0) - strong consensus (100% agreement)

12. Do organizational changes in nutritional support (e.g. intervention of a steering committee, implementation of protected mealtimes, different budget allocation) versus no changes improve outcomes of polymorbid inpatients?

Procedure of intervention

Recommendation 12.1

Organizational changes in nutritional support provision should be implemented for polymorbid medical inpatients who are malnourished or at risk of malnutrition. In particular, interventions that ensure the provision of fortified menus for at-risk patients, establishing a nutrition support team and the use of multi-disciplinary nutrition protocols should be implemented.

(Grade of recommendation B) - strong consensus (100% agreement)

a) Does underlying disease have an impact on expected outcome from nutritional support?

Statement a.1.

The severity of acute-phase response may be used by clinicians as part of the criteria for selecting patients for nutritional screening, follow-up, and intervention.

(Level of evidence 1+) - strong consensus (100% agreement)

Statement a.2.

Inadequate nutritional intake is common, and patient factors contributing to poor intake should be considered in designing nutritional interventions. Energy and protein intake are frequently inadequate to meet requirements in most older acute medical inpatients, worsening malnutrition during hospitalization and leading to poor outcomes. Poor intake is associated with several common patient/environmental characteristics, such as disease severity, symptoms compromising intake, anorexia, bedridden, hospital routines, dietary habits and possible therapeutic diets adopted at home.

(Level of evidence 4) - strong consensus (100% agreement)

Non-PICO questions, under section "Discussion"

b) How long should nutritional support be given in order to have an impact on the clinical course in a polymorbid patient?

Statement b

Although there is evidence to recommend the continued nutritional support post-hospital discharge on polymorbid medical inpatients who are malnourished or at risk of malnutrition, the ideal duration of the intervention has not yet been determined.

(Level of evidence 4) - strong consensus (95% agreement)

c) Are there risks of polypharmacy and drug-nutrient interaction in polymorbid inpatients?

Statement c

In polymorbid medical inpatients there is an important possibility of drug-drug or drug-nutrient interactions that needs to be taken into account, by establishing a pharmacist-assisted management plan for any interactions.

(Level of evidence 3) - consensus (90% agreement)